SIX CHILDREN WITH COUGHS *

The Second Diagnosis

SIMON YUDKIN
M.B., Ph.D. Lond., M.R.C.P., D.C.H.
CONSULTANT PÆDIATRICIAN,
WHITTINGTON HOSPITAL, LONDON, N.19

IN the days when I was a resident there used to be a rule that all symptoms and signs in a sick person should, if possible, be grouped together into one diagnosis. This useful, though somewhat overworked, rule has now been almost completely superseded; and it is not uncommon in patients' summaries or in postmortem reports to see a list of eight or even ten diagnoses. Nevertheless I suggest that most patients are still not adequately diagnosed. For all patients coming to a doctor there are two groups of diagnoses. One group answers the question, "What is the matter with the patient?"; the other, "Why is the patient consulting you now?"—or, in pædiatrics, "Why is this child being brought to you at this moment?" These two groups of diagnoses can be illustrated by 6 children who could be matched in any pædiatric outpatient department or indeed in any doctor's surgery.

* * *

Case 1.—A young lad of six was brought by his mother who said that he often had coughs and colds. He had recently started school and seemed to have the recurrent infections so common in children mixing with many others for the first time. But when he was undressed and I was examining his chest his mother said, "Don't you think he's too thin, doctor?"

After some time in practice one learns not to answer a question of this sort. Instead I countered, "Why do you ask?" She then told me that her mother-in-law was always complaining that the boy was too thin, and objecting to the way that she looked after him. I soon realised that mother-in-law and daughter-in-law shared a house, but very little else, and the boy was one of many subjects of conflict.

The diagnosis seems obvious—recurrent respiratory infection due to frequent exposure at school. But equally important is "Why was he brought to see me?" The answer is that the mother wanted support in her arguments with her mother-in-law on whether the child was being properly looked after. Both diagnoses are important, the second perhaps more so than the first.

Case 2.—Another six-year-old boy often had coughs. He, too, looked rather thin and his mother said, as he was being examined, "He looks so thin, doctor, I'm sure he's lost weight, and his pyjamas get wringing wet at night because he sweats such a lot." The first and straightforward diagnosis was the same as in the first case—recurrent respiratory infection. But the clue to the second diagnosis was provided by the mother's history. Sweating at night is associated in the lay mind with pulmonary tuberculosis; the mother's sister had had tuberculosis as a child; and the mother was excessively worried in case her child also had the disease. This was why the child was brought to see me.

Case 3.—Another six-year-old had had several coughs. He was not very ill, but his mother seemed very persistent, and in the history she said dramatically, "You can hear him breathe from the next room when he's coughing at night." This boy, too, had recurrent respiratory infection; but there was no evidence of asthma, in spite of the mother's statement, though this was why she had brought him. There was a long family history of asthma, and a grandmother had died of it, though her illness was clearly different from childhood asthma.

Case 4.—A girl of six had had many coughs and colds. She looked sad with straight, lank hair, untidy, and not too well cared for; but her mother's clothes and elaborate hair-do showed that for some things at least there was money to spare. I could not find much physically wrong. As I wrote my notes, the mother said, "Don't you think she ought to go away for a convalescent holiday, doctor?" I parried, "Why do you think it will do her good?" "Well, last time she went she was so much better." It transpired that the girl had already been for a convalescent holiday twice, and away from home six times in all in her short life. In her first year she was in hospital twice for several months with gastroenteritis. The mother had little affection for the child; she obviously regarded her as a nuisance, and took every opportunity of getting rid of her. A convalescent holiday might have improved her cough; but her debility was not due to infections or to not having a holiday, but to too little attention and affection at home. The mother's reason for bringing her was to see whether she could be sent away.

Case 5.—A six-year-old boy, who had had coughs and colds, seemed perfectly normal; but his mother said, "He's so small and skinny, doctor. Will you tell him he's got to eat? He never touches greens. I'm sure that's why he's always catching cold." This battle over food had begun very early. The mother thought the respiratory infection a perfect weapon with which to threaten him and make him eat. She was now trying to enlist my aid. The first diagnosis was recurrent respiratory infection; but the second was the battle over the child's feeding habits.

Case 6.—A little boy, who looked very well indeed. His mother said he had repeated coughs and colds. When I asked him to undress, his mother immediately began to help, while he did nothing. I asked what was bothering her and she said, "Well, doctor, the school keeps complaining that he's always being kept away, but he's always getting colds and I have to keep him at home". She had already been to three consultants; each had tried to reassure her, but she continued to keep the child away from school on almost any excuse. The ordinary diagnosis was a very mild respiratory infection; but this mother had obtained a letter from her doctor to come to a hospital outpatient department to get support for keeping her child at home. She certainly needed help, but not for that.

* * *

In all 6 the ordinary diagnosis was much the same; and yet each was brought for quite a different reason. In all of them the reason was important. In none was it mainly to do with the cough. In all these children, therefore, there were two major diagnoses: the first—What was the matter with the child?; the second—Why were the parents consulting me at that time? Why did the general practitioner make the appointment?

It may be argued that all this is perfectly obvious, and that every doctor takes it into account. Sometimes, of course, it *is* obvious. Doctors know that a parent complaining of a child's cough is likely to fear that he may have tuberculosis; they would say something like "Of course, mother, he hasn't got tuberculosis." When a child in summer had headache, pain, or fever, the parent must be reassured about poliomyelitis. The good general practitioner often does this automatically; but many doctors do not. The second diagnosis is often not so obvious,

*Based on a lecture given at Stanford University Medical School, California, U.S.A.

and it needs to be consciously and deliberately borne in mind.

Some would consider this all far-fetched. With acute illnesses especially, a parent's anxiety may seem rational and proportional to the severity of the illness. Sometimes the first and second diagnosis are the same—as, for example, when a school doctor hears a heart murmur and the parent comes to see the specialist about this particular problem. But this is not always so even when a child is acutely ill. Often the parents are particularly anxious about a child's illness because another child or a relative had a similar illness and died. Or a general practitioner might ask me not to use particular words which have a special meaning for the family—to say " congestion of the lungs ", for example, instead of " pneumonia ". Sometimes a parent seems remarkably *unconcerned* about a child's evident poor health. Especially when children have trivial complaints we should wonder why the child has been brought to the doctor at this particular time with symptoms that may have been present for, say, five years. Was it the general practitioner who wanted a second opinion, or did one of the parents insist on a hospital appointment? Why is one child brought when three others at home seem to have a similar history?

* * *

Am I overstressing this idea of a second diagnosis? I think not. It is often the main reason for patients being brought to the doctor. We can observe how persistent and dissatisfied a mother is when the second diagnosis is ignored, and the tremendous relief when anxiety is brought into the open and dealt with. How many patients are taken to several doctors without apparent benefit, simply because nobody thought of asking why they have come? Even when the ordinary traditional diagnosis is clinically important, it may be necessary to deal with the second before a parent can be helped to deal with the clinical problem. The second diagnosis may colour the history given by the mother. The explanation offered by the parents for a child's illness is often one which fits their own ideas of causation and their own medical theories and which reflects their own dislikes or fears. For example, in the history of a child with abdominal pain, the mother may say, " She was pushed over in school last week, and the pain has come on since." In fact the pain was present before the fall, but the mother thought that the fall offered a satisfactory explanation, which allowed her to blame somebody for the abdominal pain, so that she need not feel that her own care of the child was at fault. In another child a cough was said to have started after diphtheria immunisation. This may have been chronologically true, but was clearly not the real cause. But the mother had had to be persuaded to have her child immunised, and she gave the history accordingly.

Other common reasons for coming are: because the doctor wanted an X-ray; because a neighbour thought it was whooping-cough; because the mother is unable to go to work because the child has been sent home from school. There are children causing great anxiety because of backwardness in development which the mother has noticed but which she hopes that you will not observe and hence, by implication, deny. Some children are taken from doctor to doctor in the hope that one will take their tonsils out—a form of aggression against one's children which is still socially acceptable.

A further reason for the second group of diagnoses is a failure of communication between doctor and patient. The doctor who casually says, after a child has had pneumonia, " See that he doesn't catch colds ", may be adding to guilt over the possibility that the child originally caught a cold and pneumonia because of the parents' lack of care. And as if any of us knew how to stop people catching cold! Similarly with " Be sure he doesn't lose weight! " Clearly, many statements attributed to doctors are never made, or at any rate are grossly misinterpreted; but undoubtedly we can add to parents' anxieties by ill-timed, ill-judged, and thoughtless remarks.

Some diagnoses in the second group spring from local and general mythology or folklore, old as history and new as commercial television, which provides most of the laity with curious but deeply held beliefs about medical conditions. Does not heart-disease, in most families, bring to mind a dreadful malady which may end in sudden death? No wonder the school doctor who says, " I've found a heart murmur. You'd better go to hospital to find out more about it ", creates more anxiety than he expects. There is also the belief that a child who has had a chest infection may have " a weak chest ". What this means I have never discovered; but it gives parents a pretext for considerable anxiety, much overdressing, and excessive overprotection. Besides the general mythology of illness in a particular country, every locality and every class has its own specific mythology. A doctor in practice gradually absorbs the local mythology and learns to understand the phrases his patients use to describe their own symptoms or special worries. A doctor who practises without learning the local myths and language is practising in blinkers and misses a great deal his patients tell him.

* * *

How, then, can we begin to find out why a patient came to see us? Some of the reasons are common, and we think of them automatically after being in practice for a little while. Some others we can guess if we know the family well. In this respect a good family practitioner is in a very much better position than a hospital consultant to know why the patient has come. I have already mentioned fear of tuberculosis, poliomyelitis, and appendicitis. Another example are the Cypriot mothers who bring their children because they look pale and are not as fat as their parents would like. There is nothing the matter with most of them. But the parents are thinking of thalassæmia, and a discussion on feeding will not satisfy them. They want to be reassured that their child has not got thalassæmia.

The most important way of finding out why patients come is to take a careful history. Doctors should learn to listen, particularly to the things the mother emphasises, and to the details of the family history. They must also note what she leaves out. It is important to listen rather than to ask; only rarely does a frontal assault provide a good history. To paraphrase Dr. Balint (1957): " If you ask questions you get only answers." What the doctor should really be trying to do is to help parents to talk. This is difficult in most hospital outpatient departments, more so when students are present. Yet they must be taught. Some privacy, or at any rate an atmosphere of privacy, is essential; this is possible even in teaching-hospital practice, as Sir James Spence brilliantly showed in his outpatient clinics in Newcastle. We must learn to

appreciate not only words but also appearance, behaviour, gestures, and facial expression (Meares 1960). I have found some openings quite helpful even in a crowded and rushed outpatient department. For example, it is better to open the interview with a parent by saying, " Please tell me about John ", rather than " What is the matter with John ? " Often the story elicited is very different from the symptoms described in the doctor's letter. " What is particularly bothering you about him ? Do you think it has got worse lately ? What do you think might have caused the trouble ? " These and other " open-ended " questions offer the parent an opportunity to talk more freely. But the attitude and atmosphere in the consulting-room matters more than any questions asked, or any techniques adopted. Time is important, and encouraging silences by the doctor stimulates the parent to tell of things that she might not otherwise mention. The most important statement of the interview is often made at the very end. Notice what a mother says as she is helping her child to dress or getting up to leave: it may often be a clue to the second diagnosis. If the first interview leaves the subject unfinished, a second consultation, preferably with both parents and without the child, may be rewarding.

I shall be accused of suggesting that doctors should spend time when time is the one thing we cannot spare; but do we not waste more time rushing through twenty-five new outpatients, nine-tenths of whom are unhappy because we have not answered their real questions, rather than seeing ten outpatients and allowing them more time to tell us why they came ? If we do not satisfy them, some of those parents will go to another doctor for a further session, hoping that he will at last answer their questions.

I shall also be accused of prying. If patients are worried, why should they not *tell* the doctor ? Why should it be necessary for the doctor to find out what their real anxiety is ? Experienced general practitioners will know how difficult it is for parents, or patients, to ask, or sometimes even to know what it is that bothers them, or what brought them to the doctor. How true this is we often discover if we have allowed enough time, and a parent says, with a look of profound relief, " I suppose that's really what I've been bothered about all the time. I didn't realise it myself."

I am not suggesting that every doctor needs to be a psychiatrist or even " psychiatrically orientated " as our American friends would say. Nor am I suggesting that a general practitioner, or a pædiatrician or other consultant, needs to make a full appraisal of all the problems that affect a parent. But many problems raised by the second diagnosis can be helped by simple explanation or reassurance. Many other patients are helped simply by having been able to find a ready and sympathetic listener. Sometimes assessment will show the need for help from a psychiatrist or from a social agency. At least we shall know what needs to be treated and not waste time and energy making many pointless investigations, or offering assurances that mean nothing.

* * *

For every patient who comes to a doctor, two questions must be answered: " What is the matter with the patient ?' and " Why has he come ? " The first we are taught about and trained to deal with. To deal with both is the beginning of real medicine. I am afraid it has taken me many years to learn to ask, let alone answer, the second question. I am humbly submitting that the need for the second question should be taught earlier.

I would like to thank Dr. Robert H. Alway, the dean, and Dr. Norman Kretchmer, professor of pædiatrics, Stanford University Medical School, for inviting me to lecture. I would also like to thank my registrars and house-physicians for reading and criticising the draft.

REFERENCES

Balint, M. (1957) The Doctor, His Patient, and the Illness; chap. 3. London.
Meares, A. (1960) *Lancet*, i, 663.

THE HYPOGLYCÆMIC ACTION OF PHENFORMIN

Studies in Diabetics after Short-term Therapy

W. J. H. BUTTERFIELD
O.B.E., B.M. Oxon., F.R.C.P.
PROFESSOR OF EXPERIMENTAL MEDICINE IN THE UNIVERSITY OF LONDON

I. KELSEY FRY
B.M. Oxon., M.R.C.P.
RESEARCH FELLOW

M. J. WHICHELOW
B.A. Cantab.
RESEARCH ASSISTANT

DEPARTMENT OF EXPERIMENTAL MEDICINE
GUY'S HOSPITAL, LONDON, S.E.1

THE search for a satisfactory oral hypoglycæmic agent is far from new. After Müller (1877) and von Noorden (1901) had tried various effective salicylate compounds, Watanabe (1918a and b) gave the first account of the hypoglycæmic action of guanidine, showing that 150–200 mg. per kg. lowered the blood-sugar in rabbits. Since this compound produced toxic neurological signs, Frank et al. (1926) tried to alter the molecular structure of guanidine while retaining the hypoglycæmic properties. Decamethylene diguanidine was synthesised and tried under the name synthalin A (Frank et al. 1926). This compound and the related substance, isoamyleryl guanide (synthalin B), lowered the blood-glucose level in certain diabetics, but when gastrointestinal disturbances and abnormal liver function were observed it was suspected that their hypoglycæmic action was a manifestation of liver damage. Ideas of practical oral therapy in diabetes were set aside and dietary restrictions and insulin treatment held sway until Janbon et al. (1942) observed hypoglycæmia among patients treated with isopropylthiodiazol (I.P.T.D.). Loubatières (1944, 1946) showed that the hypoglycæmia was probably due to the stimulation of insulin production by the β-cells of the pancreas. Successful oral antidiabetic therapy from I.P.T.D. derivatives, notably the sulphonylurea, tolbutamide, followed (Levine and Duncan 1956).

In view of the use of guanidines in long-term therapy without toxic effects in other conditions—proguanil hydrochloride in malaria and chlorhexidine cream in burns—it is not surprising that fresh attempts should have been made to produce new safer guanides with hypoglycæmic actions. The present compounds are not *di*guanides like synthalin, but *bi*guanides—that is to say, the guanide groups are in apposition rather than at either end of the compound. Phenethylbiguanide (phenformin, ' Dibotin,' or D.B.I.) was the first of this group to be tested. The formulæ and relationships between structure and hypoglycæmic action of the above compounds, including phenformin, have been reviewed recently by Mahler (1960), and clinical and laboratory studies in the U.S.A. have been reported extensively after a recent symposium (Marble 1960).

The hypoglycæmic action and relative non-toxicity of phenformin has been confirmed in animals by Unger et al.

(1957) and in clinical trials by Pomeranze et al. (1959). The mechanism of action has been deduced largely from studies using animal tissues, although some important species differences have already been recognised: for example, phenformin lowered the blood-sugar in guineapigs but not in dogs (Unger et al. 1957) or man with normal carbohydrate metabolism (Fajans et al. 1960). Clarke and Forbath (1959) showed that phenformin added to the incubation medium increased glucose uptake by the rat diaphragm, and Williams et al. (1957) suggested that this was due to the inhibition of aerobic respiration. More recently Wick et al. (1958) using the rat epididymal fat pad found that phenformin inhibited the succinic-oxidase system, and Kruger et al. (1960), using rat kidney mitochondria, reported that phenformin decreased oxygen uptake. Hypotheses based on such experiments are open to grave criticism, however, since the concentrations used were several hundred times greater than obtained with therapeutic doses in man.

When phenformin was made available for use in the management of diabetes in this country, we therefore investigated its mode of action in our patients during treatment. As with a previous study of the sulphonylureas (Butterfield et al. 1957) several modes of hypoglycæmic action had to be considered. It seemed possible that phenformin in therapeutic doses might

(1) Interfere with absorption of foodstuffs, especially since gastrointestinal disturbances were a prominent side-effect.

(2) Enhance the action of exogenous or endogenous insulin—for example, by inhibiting insulinase, as suggested by the findings of Williams et al. (1959) using very high doses in experimental animals.

(3) Interfere with liver action, glycogenolysis in particular, an important consideration in view of the hepatotoxic properties ascribed to the synthalins.

(4) Increase glycolysis by inhibition of oxidative metabolism, since, during the course of these studies, Fajans et al. (1960) reported that phenformin caused diminished tolerance to an intravenous load of sodium pyruvate.

Our work falls into two parts: this paper deals with investigations of the effect of phenformin on the *systemic glucose* and *pyruvate blood-levels* under various circumstances. A later paper will be concerned with more detailed studies about the direct effect of phenformin on the *glucose metabolism* of the *forearm tissues*.

Design of Experiment

The purpose was to explore the mode of action of phenformin by several tests performed before and after 7–10 days' therapy in a variety of patients. Sixteen diabetics, aged 21–76, with diabetes of from 0 to 26 years' duration were investigated in hospital. In five patients diabetes had begun under 25 years of age, with classical symptoms of onset; they were insulin-dependent and prone to ketosis. Eleven cases were aketotic adult-type diabetics.

Procedures

(a) *Chemical.*—All patients were admitted to the metabolic ward of Guy's Hospital for the duration of the investigation. As far as possible they were up and about to match their usual daily exercise. Their usual diet, ordered during attendance at the diabetic clinic, was maintained but any insulin prescribed was given as the soluble form for at least 48 hours before the present studies began, usually longer. Aliquots of 24-hour urine collections were used to determine daily glycosuria levels. The urine was also tested five times daily at 6 A.M., 10 A.M., 2 P.M., 6 P.M., and 10 P.M. for glucose and acetone ('Acetest'), the bladder being emptied half an hour before each collection.

TABLE I—CLINICAL DETAILS OF THE DIABETIC SUBJECTS, GRADED ACCORDING TO THE PERCENTAGE FALL OF FASTING BLOOD-SUGAR (F.B.S.) AFTER PHENFORMIN

Case	Sex	Age	Diabetes recognised for (yr.)	Body type	Previous tendency in ketosis	Daily insulin dose (units)	F.B.S. before phenformin	% fall of F.B.S.'
1	F	64	4	Pl	..	Nil	236	46
2	M	66	2	Th	..	Nil	137	45
3	F	66	6	Ob	..	Nil	250	42
4	F	65	1	Ob	..	Nil	216	41
5	F	55	1	Ob	..	Nil	225	41
6	M	67	23	Th	+	32 IZS	179	26
7	M	45	1	Th	..	Nil	156	25
8	M	42	4	Th	..	Nil	152	28
9	F	32	12	Th	+	44 Lente	296	20
10	F	76	2	Ob	..	Nil	262	14
11	F	55	1	Th	..	Nil	276	6
12	F	66	9	Ob	..	Nil	203	3
13	F	38	26	Th	+	52 IZS	503	−6
14	M	21	4	Pl	+	90 S	398	−20
15	M	35	11	Th	+	72 S	439	−25
16	F	28	11	Pl	+	30 S	287	−26

Case 1, 6, and 15 showed clinical evidence of diabetic neuropathy.
Pl = plump, Th = thin, Ob = obese.

Fasting blood-sugars were taken as appropriate. Phenformin was started in doses of 25 mg. two, three, or four times a day, given with meals, increasing to 50 mg. three or four times a day as quickly as tolerated. Nausea, when it occurred, was treated with antihistamines. After 7–10 days' therapy follow-up tests were performed, 50 mg. of phenformin being given three hours before they were started. The insulin dose was reduced during phenformin therapy whenever the patients showed a tendency towards better control. Insulin was not given on the mornings of any tests, before or after phenformin therapy.

(b) *Tests.*—Capillary blood samples for glucose estimations were taken during the following tests: glucose (50 g. by mouth) (G.T.T.); glucose-insulin (50 g. by mouth and 7 units intravenously) (G.I.T.T.); and intravenous glucose-insulin (20 g. and 7 units both intravenously) (I.V. G.I.T.T.). The tests were performed in fasting subjects (Butterfield et al. 1957). Venous samples for pyruvate estimation were taken at 0 and 60 minutes in the oral G.I.T.T., the rise of pyruvate being taken as an index of the amount of glucose entering the cells during this time (Butterfield and Thompson 1957).

To examine oxidative metabolism of the peripheral tissues, we studied the uptake of glucose and pyruvate in the forearm during glucose-insulin tests before and during phenformin therapy in three patients with high pyruvate values. The method involved simultaneous arterial and venous determinations of glucose and pyruvate, and concurrent assessment of forearm blood-flow (see Butterfield and Holling 1959).

To assess the availability of liver glycogen before and after phenformin therapy a glucagon test, using more physiological

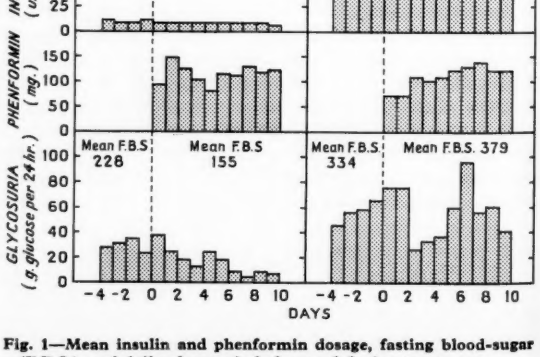


Fig. 1—Mean insulin and phenformin dosage, fasting blood-sugar (F.B.S.), and daily glycosuria before and during treatment.

TABLE II—MEAN GLUCOSE LEVELS IN RESPONDERS AND NON-RESPONDERS DURING GLUCOSE-TOLERANCE TEST AND GLUCOSE-AND-INSULIN-TOLERANCE TESTS BEFORE AND AFTER PHENFORMIN

—	Test		F.B.S. mean fasting (mg. per 100 ml.)	Mean rise at		
				30 min.	60 min.	90 min.
Responders (7 patients)	G.T.T.	Before	222	71	96	120
		After	143	67	95	136
	G.I.T.T.	Before	224	18	35	79
		After	152	10	22	49
Non-responders (5 patients)	G.T.T.	Before	321	65	99	132
		After	369	50	66	97
	G.I.T.T.	Before	322	−8	−2	1
		After	363	−46	−63	insufficient data

doses than usually described, was performed. This assessment depends upon the rise of blood-sugar produced by glucagon in saline, infused at 2 μg. per min. for 20 minutes. (Butterfield et al. 1960).

(c) *Chemical.*—Glucose was estimated by a minor modification of the glucose-oxidase method of Huggett and Nixon (1957) In non-ketotic patients blood keto-acids, largely pyruvate, were estimated by the method of Friedmann and Haugen (1943). In ketotic patients, pyruvate was also estimated chromatographically by a modification of the method of McArdle (1957).

Results

Table I shows the sex, age, relevant clinical information, and insulin dosage of the diabetic patients in the study, together with the percentage drop of fasting blood-sugar after treatment. This figure was used to grade the response, patients whose mean fasting blood-sugars fell by more than 10% being classed as responders.

Fig. 1 shows the mean insulin dosage, phenformin dosage, and glycosuria for four days before the trial and for the first ten days while the patients were having phenformin, for the responders and the non-responders, with the mean fasting blood-sugars before and after treatment. The mean phenformin dosage in both groups was the same. The mean insulin dosage of the non-responders was slightly reduced during the trial. The responders showed steadily diminishing glycosuria during phenformin therapy, whereas non-responders showed a fall in glycosuria on the third day which was not maintained and reverted to previous values by seven to ten days—a phenomenon also noticed with the non-responders to the sulphonylureas (Butterfield et al. 1957).

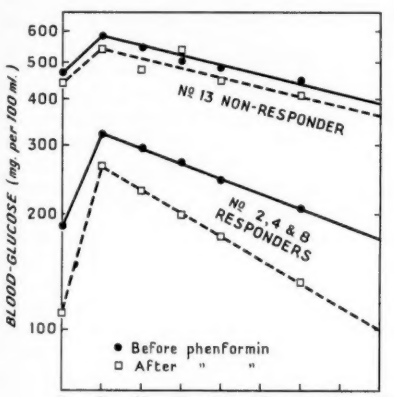


Fig. 2—Results of intravenous glucose-insulin tolerance test before and after phenformin therapy.

Table II shows, for both groups, the effect of phenformin on the blood-glucose, both fasting and during oral glucose and glucose-insulin tolerance tests. There was no change in the shape of the G.T.T. in the responders, but the rise of blood-sugar in the G.I.T.T. after therapy was less than before, suggesting increased insulin sensitivity. In the non-responders, however, the hyperglycæmia was diminished in *both* tests during treatment, which could be explained by defective glucose absorption from the gut, especially as several of these patients complained of nausea. In order to circumvene this possibility intravenous G.I.T.T.s were performed in selected cases. Fig. 2 shows the results before and after ten days' therapy with phenformin; in three patients who responded to phenformin the fall of blood-sugar was steeper after treatment than before, whereas in the non-responder the slope was unaltered.

Fig. 3 shows the hyperglycæmic effects of the glucagon infusion which was greater after treatment for both groups but especially so in the responders.

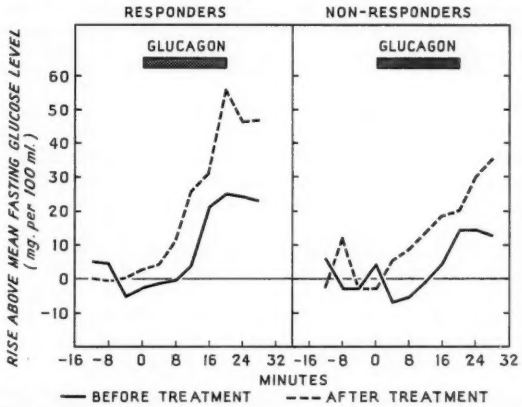


Fig. 3—Effect of glucagon infusion on blood-sugar levels before and after phenformin treatment in 7 responders and 5 non-responders.

Fig. 4 shows the blood-pyruvate levels in the fasting state and at 60 minutes after glucose and insulin. After treatment both groups showed a slight rise in the fasting level; the responders also showed a greater rise at 60 minutes.

Fig. 5 shows the incidence of ketosis in those patients who did not lose weight during the drug trial. There was a rise in ketosis during successful therapy, despite the fact that the blood-sugar and glycosuria were falling. Non-responders also showed a rise in ketosis towards the end of the trial period.

Table III summarises the results of studies of peripheral pyruvate metabolism during G.I.T.T.s. No effect of phenformin on pyruvate uptake is apparent in the fasting state, or during the tests, although the glucose uptake was increased by phenformin. It should be noted that the arterial pyruvate level exceeded the venous level during the tests.

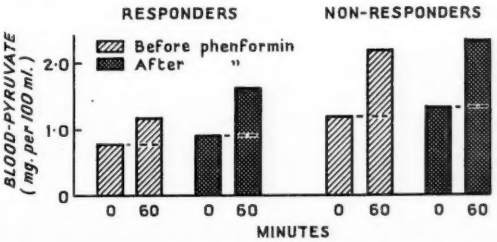


Fig. 4—Mean venous pyruvate levels in fasting state and at 60 min. after glucose and insulin in 6 responders and 5 non-responders before and after phenformin therapy.

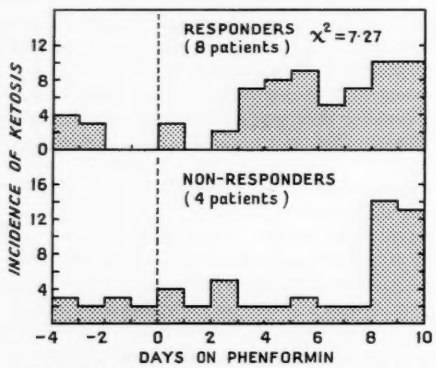


Fig. 5—Incidence of ketosis (total number of urine samples per day showing positive Acetest ++) before and during treatment in those patients of both groups who did not lose weight during therapy.

Discussion

Phenformin is clearly a potent hypoglycæmic substance effective in most diabetics we have tested. Unfortunately, treatment was sometimes associated with nausea and vomiting, and in this respect our findings confirm those of many other workers (Krall et al. 1958). Perhaps these side-effects could have been avoided by lower starting doses and slower increases.

Phenformin, Sulphonylurea, and Insulin Compared

Insulin, the sulphonylureas, and phenformin all lower the blood-sugar and reduce glycosuria effectively in selected diabetics. Furthermore the sulphonylureas and insulin increase the amount of liver glycogen released by an infusion of glucagon and our results show that phenformin has a similar effect.

Insulin is believed to act by increasing cell permeability to glucose and the sulphonylureas by stimulating the secretion of insulin from beta-cells. Certain subtle differences between these agents and phenformin indicate that it must have a separate mode of action. Firstly, the three compounds are not interchangeable, since some patients who responded to phenformin in this trial had failed previously on sulphonylureas (cases 6 and 9) and vice versa (case 12) and in none of our insulin-dependent diabetics could we completely replace the hormone with phenformin. Secondly, phenformin enhanced the response to insulin in the oral and intravenous glucose-insulin tests in those patients who were successfully treated, and caused higher pyruvate levels and sometimes altered gastrointestinal absorption in patients of both groups—none of which effects were observed with the sulphonylureas (Butterfield et al. 1957). Thirdly, there are important points of contrast between phenformin and insulin; phenformin does not lower the blood-sugar in normal subjects (Fajans et al. 1960) and its hypoglycæmic action in diabetes is associated with an increased incidence of acetonuria. Pomeranze et al. (1959) suggested that this be attributed to starvation from impaired gastrointestinal absorption. We are not convinced by this argument, since our cases showed acetonuria without losing weight. The latter might be due to fluid retention, but other possibilities exist—the renal clearance of acetone might be altered or phenformin might initiate the release of fat-mobilising hormone (Chalmers et al. 1960).

TABLE III—STUDIES OF GLUCOSE AND PYRUVATE METABOLISM OF FOREARM TISSUES DURING G.I.T.T.S IN THREE INSULIN-DEPENDENT DIABETICS BEFORE AND DURING PHENFORMIN THERAPY

—	Fasting	During glucose-insulin test	
		30 min.	60 min.
Before phenformin			
Arterial pyruvate ..	1·48	3·11	3·57
Venous pyruvate ..	1·30	2·10	2·57
Pyruvate uptake ..	0·66	2·79	3·40
Glucose uptake ..		← 18 →	
During phenformin			
Arterial pyruvate ..	1·74	2·83	3·65
Venous pyruvate ..	1·29	2·45	3·02
Pyruvate uptake ..	0·60	1·67	3·22
Glucose uptake ..		← 35 →	

Blood pyruvate values in mg. per 100 g. blood
Pyruvate uptake in µg. per 10 ml. forearm per min.
Glucose uptake in mg. per 100 ml. forearm over one hour.

To us, therefore, a more plausible explanation of our findings is that phenformin enhanced the action of insulin. This would account for the greater sensitivity to insulin found in the tests during treatment. The increased amount of glucose leaving the circulation during the glucose-insulin test after therapy would also cause the greater rise of pyruvate observed at 60 minutes. Furthermore, if one accepts that insulin therapy increases the amount of glycogen in the diabetic liver (Renold et al. 1955, de Duve 1956), our hypothesis about phenformin would account

Hypoglycæmic Action of Phenformin

Successful phenformin therapy in our patients cannot be attributed to impaired absorption of glucose by the gut, nor to increased urinary excretion. The results of the glucagon tests show that phenformin does not interfere with the action of glucagon, nor is there any evidence that glycolysis or glucose-6-phosphatase were impaired—indeed, it might be argued that liver glycolysis per se cannot have been stimulated either, since there was more available glycogen after treatment. It also seems unlikely that phenformin acts in a direct way by increasing glucose uptake, since there was no improvement in glucose tolerance in the cases who responded. Nor are we persuaded that phenformin brings about its hypoglycæmic action by stimulating anærobic glycolysis elsewhere than in the liver. We agree with Fajans et al. (1960) who, using higher doses than we did, showed that phenformin caused a significant fall of blood-sugar and a rise of venous pyruvate levels, which they attributed to inhibition of Krebs-cycle enzymes. It seems to us, however, that the results of the present studies of pyruvate and glucose uptake argue against the theory that such a block might cause hypoglycæmic activity. We find no evidence after phenformin therapy of a block to pyruvate metabolism in the peripheral tissues in the fasting state or during G.I.T.T.S (table III), although, as has been reported previously (Butterfield et al. 1958) the peripheral tissues certainly share in the hypoglycæmic response. The high pyruvate levels in the arterial blood during G.I.T.T.S shed some light on the problem. The rise of venous levels detected by Fajans et al., and confirmed here by the results in fig. 4 and table III, must have reflected glucose entering some central tissue or tissues in large amounts under the influence of insulin, and being degraded to pyruvate before diffusing back into the systemic circulation as pyruvate thereby raising the arterial (and venous) levels during the tests. It may be that, apart from its hypoglycæmic action associated with effects in the periphery, phenformin affects some other organ, such as the liver, so that it releases pyruvate into the circulation under the circumstances of our tests, and presumably failed to take it up under the conditions of Fajans and his colleagues.

for the improved hyperglycæmic response to the glucagon infusions.

However, in view of the conflicting evidence about the direct effects of phenformin on the glucose uptake by animal tissues (Steine and Williams 1958, Wick and Larson 1958, Clarke and Forbath 1959) and man (Madison and Unger 1960), further investigations are being undertaken to decide whether therapeutic doses have any direct action on muscles in man or enhance the action of insulin in the peripheral tissues.

Summary

To investigate some possible modes of action of phenformin (phenethylbiguanide, D.B.I.) in clinical doses as used in man, 16 diabetics of various clinical types aged 21 to 76 were admitted to hospital and subjected to tests involving the response to glucose, insulin, and glucagon before and after 7–10 days' therapy with phenformin. In 10 cases phenformin improved fasting blood-sugar and urinary glucose output, but side-effects included nausea and unexplained ketosis without weight-loss.

The results showed several strong contrasts to those in a similar previous study of the action of the sulphonylureas, oral and intravenous glucose-insulin tolerance improved, and blood-pyruvate levels rose. The response to glucagon reverted towards normal after successful phenformin.

It is tentatively concluded that phenformin augmented the action of insulin.

We wish to thank Dr. Christopher Hardwick for permission to study cases under his care at Guy's Hospital, and to Sister W. Watson and the nursing staff of William Gull Ward for their help and cooperation. We are indebted to Mrs. Annette May for technical assistance. One of us (M. J. W.) was supported by a grant from the Medical Research Council. Dr. W. F. Simpson, of Duncan Flockhart Ltd., Edinburgh, kindly provided the phenformin for these studies and Mr. E. A. G. Cook, of Eli Lilly, supplied the glucagon-free insulin and glucagon.

REFERENCES

Butterfield, W. J. H., Camp, J. L., Hardwick, C., Holling, H. E. (1957) *Lancet*, i, 753.
— Fry, I. K., Holling, H.E. (1958) *Diabetes*, **7**, 449.
— — Whichelow, M. J. (1960) *Guy's Hosp. Rep.* **109**, 95.
— Holling, H. E. (1959) *Clin. Sci.* **18**, 147.
— Thompson, R. H. S. (1957) *ibid.* **16**, 679.
Chalmers, T. M., Pawan, G. L. S., Kekwick, A. (1960) *Lancet*, ii, 6.
Clarke, D. W., Forbath, N. (1959) *Metabolism*, **8**, 553.
de Duve, C. (1956) Ciba Foundation Colloquia on Endocrinology, **9**, 203.
Fajans, S. S., Moorhouse, J. A., Doorenbos, H., Louis, L. H., Conn, J. W. (1960) *Diabetes*, **9**, 194.
Frank, E., Nothmann, M., Wagner, A. (1926) *Klin. Wschr.* 2100.
Friedmann, T. E., Haugen, G. E. (1943) *J. biol. Chem.* **147**, 415.
Huggett, A. St. G., Nixon, D. A. (1957) *Lancet*, ii, 368.
Janbon, M., Chaptal, J., Vedel, A., Schaap, J. (1942) *Montpellier méd.* **21-22**, 441, 489.
Krall, L. P., White, P., Bradley, R. F. (1958) *Diabetes*, **7**, 468.
Kruger, F. A., Skillman, T. G., Hamwi, G. J., Grubbs, R. C., Danforth, W. (1960) *ibid.* **9**, 170.
Levine, R., Duncan, G. G. (1956) *Metabolism*, **5**, 721.
Loubatières, A. (1944) *C. R. Soc. Biol., Paris*, **138**, 766, 830.
— (1946) Thèse Doct. Sci. Naturelles, Montpellier.
McArdle, B. (1957) *Biochem. J.* **66**, 144.
Madison, L. L., Unger, R. H. (1960) *Diabetes*, **9**, 202.
Mahler, R. F. (1960) *Brit. med. Bull.* **16**, 250.
Marble, A. (1960) *Diabetes*, **9**, 225.
Müller, G. (1877) *Berl. klin. Wschr.* **14**, 29.
Pomeranze, J., Mouratoff, G. T., Gadek, R. J., King, E. J. (1959) *J. Amer. med. Ass.* **171**, 252.
Renold, A. E., Hastings, A. B., Nesbett, F. B., Ashmore, J. (1955) *J. biol. Chem.* **213**, 135.
Steine, D. F., Williams, R. H. (1958) *Clin. Res.* **6**, 55.
Ungar, G., Freedman, L., Shapiro, S. L. (1957) *Proc. Soc. exp. Biol., N.Y.* **95**, 190.
von Noorden, C. H. (1901) Die Zuckerkrankheit und ihre Behandlung. Berlin.
Watanabe, C. K. (1918a) *J. biol. Chem.* **33**, 253.
— (1918b) *ibid.* **34**, 65.
Wick, A. N., Larson, E. R. (1958) *Clin. Res.* **6**, 91.
— — Serif, G. S. (1958) *J. biol. Chem.* **233**, 296.
Williams, R. H., Martin, F. B., Henley, E. D., Swanson, H. E. (1959) *Metabolism*, **8**, 99.
— Tyberghein, J. M., Hyde, P. M., Nielsen, R. L. (1957) *ibid.* **6**, 311.

ALDOSTERONE EXCRETION IN DISEASE OF THE PRETECTUM

DOROTHY T. KRIEGER
M.D. Columbia
RESEARCH ASSISTANT

AKIRA SAITO
Ph.D. Osaka
RESEARCH ASSISTANT

HOWARD P. KRIEGER
M.D. Long Island
ASSOCIATE ATTENDING NEUROLOGIST

From the Endocrine Research Laboratory and Clinic of the Department of Medicine, and from the Department of Neurology of the Mount Sinai Hospital, New York City

THE mechanism (or mechanisms) governing aldosterone secretion remains a subject of debate. The existence of a central regulatory mechanism in or near the pineal and independent of the pituitary or median-eminence area has been postulated by Farrell and his coworkers (Newman et al. 1958, Farrell 1959, 1960a and b). Davis (1959) and Ganong (1959), however, state that aldosterone secretion is depressed only by those hypothalamic lesions which involve the median eminence and concomitantly depress the secretion of hydrocortisone.

In this paper we describe studies concerned with the secretion of aldosterone and its response to sodium deprivation in two patients with disease of the central nervous system localised to the area which Farrell suggested is involved in aldosterone regulation. These patients had no evidence of other endocrinopathy. We are unaware of similar observations on comparable cases.

Methods

Chemical.—Urinary aldosterone determinations were performed by a modification of the method of Sobel et al. (1959) which is based on the Neher-Wettstein method (1956):

Separation was accomplished by means of three paper chromatograms. The solvent systems were: (1) ethylene glycol-toluene; (2) Eberlein-Bongiovanni (E_2B)-trimethylpentane-tertiary butanol-water; and (3) Bush (B_9)-water-methanol-heptane-benzene. The eluate from the final paper was used for the determination of aldosterone by development with blue-tetrazolium and tetramethyl ammonium hydroxide. The resultant solution was read at 445 mμ, 535 mμ, and 924 mμ, and the optical density was corrected by the formula:

$$\text{O.D.} = 545 - \frac{(\text{O.D. } 445 + \text{O.D. } 625)}{2}.$$

Final values were based on a standard curve obtained with pure aldosterone determined at 0·5 μg. and at 1 μg. intervals from 1 to 10 μg. Normal values for this laboratory range from 3 to 10 μg. per 24 hours.

Clinical.—Localisation of the lesion was established by clinical and radiographic techniques.

Case-histories

THE FIRST CASE

A 45-year-old woman was admitted to the Mount Sinai Hospital on Jan. 29, 1960, complaining of severe dizziness (vertigo), blurring of vision (especially on the left), double vision, and unsteady gait with veering to the left, all of 5 weeks' duration. For 2 months before admission she had been aware of diminished sensation in the left upper arm and tingling of the left side of the face. Two years previously the patient had had a left radical mastectomy for carcinoma, at which time there was no evidence of axillary involvement. The menses had been normal, but some libido had been lost during the 3 months before admission. There was no history suggestive of thyroid or adrenal dysfunction, polyuria, or polydypsia.

She was alert and well developed. The blood-pressure was 120/80 mm. Hg, the pulse-rate 74 per minute, and respirations 18 per minute. The skin was normal in texture and pigmentation. The thyroid gland was not palpable. There was a well-healed left mastectomy scar. No lymphadenopathy was noted. Pelvic examination was within normal limits.

BIOCHEMICAL FINDINGS IN CASES 1 AND 2

Case (yr.)	Age	Sex	Diagnosis	Urinary Aldosterone (μg. per 24 hr.)	Urinary 17-hydroxycorticosteroids (mg. per 24 hr.)	Urinary 17-ketosteroids (mg. per 24 hr.)	Diurnal variation of plasma 17-hydroxycorticosteroids (μg. per 100 ml.)	Serum Na (mEq. per l.)	Serum K (mEq. per l.)	Serum Cl (mEq. per l.)	Serum CO_2 (mEq. per l.)
1	45	F	Lesion in pretectal area (presumably metastatic)	Pre-radiotherapy: 2·7 2·0* Post-radiotherapy: 7·2 5·4*	5·1	12·3	4 A.M.—19·0 8 A.M.—34·6 NOON—21·4 4 P.M.— 8·5 10 P.M.—40·0	140·0	4·7	97·0	28·6
2	45	M	Lesion in pretectal area (neoplastic or hæmorrhagic)	1·6 8·0*	8·0	5·2	4 A.M.—10·0 8 A.M.—38·6 NOON—53·4 4 P.M.—27·6 10 P.M.—16·8	139·0	5·3	95·0	20·4

*These levels were obtained after the patient had been on a diet containing 17·4 mEq. sodium per day for 3 days.

The patient's mental status was intact. Fundoscopic examination showed bilateral blurring of the disc margins superiorly, more on the left than the right. The visual fields were normal. The left pupil was irregular and larger than the right. Both pupils reacted on convergence, while only the left reacted to light. Upward gaze was paralysed bilaterally. There was convergent nystagmus on attempted upward movement of the eyes, but nystagmus was not observed in any other direction of gaze. Motor examination revealed slight weakness of the left arm. All the deep tendon-reflexes were normal, and Babinski's sign was negative. Romberg's sign was positive. There was no dysdiadochokinesia. The finger-nose and heel-knee tests were normal. Sensory examination revealed slightly decreased pinprick sensitivity of the left upper arm; vibration and position sense were intact. There were no abnormal findings on carotid-artery compression.

The pertinent chemical laboratory findings are shown in table I. Other studies showed a normal hæmogram and urine analysis. The blood-urea-nitrogen, fasting blood-sugar, and serum albumin, globulin, calcium, phosphorus, and alkaline-phosphatase were all within normal limits. The radioactive-iodine uptake was 35% in 24 hours.

Radiographs of the chest and skull showed no abnormality; the sella turcica was normal in size and no abnormal intracranial calcifications were noted. The electroencephalogram was normal. Lumbar puncture revealed clear spinal fluid, with an initial pressure of 110 mm. water, which contained 108 mg. of protein per ml.; 2 lymphocytes per c.mm. were present. A right carotid arteriogram showed the vein of Galen and the middle-cerebral artery to be slightly higher than usual. Pneumoencephalography revealed symmetrical dilatation of both lateral ventricles, and slight dilatation of the third ventricle which was deviated to the left posteriorly. On lateral projection thinning of the aqueduct could be seen near the posterior portion of the third ventricle. Myeloencephalography (figs. 1 and 2) confirmed the findings of the pneumoencephalogram, and also demonstrated a ventral displacement at the junction of the third ventricle and aqueduct, with deviation of the aqueduct itself to the left.

The disturbances in ocular motility, and the radiological findings, led to the diagnosis of a small lesion in the pretectum.

Course

The patient received cobalt-60 therapy, with a total dose of 5000r, to the pretectal area over a 2-month period. When she was seen 6 weeks after the initiation of therapy she reported less subjective visual blurring and ataxia. Both pupils were now equal and reacted well to light. Upward gaze was still paralysed, but convergent nystagmus on attempted upward gaze was much less marked. The weakness and sensory defects in the left upper arm had lessened. Romberg's sign was now negative.

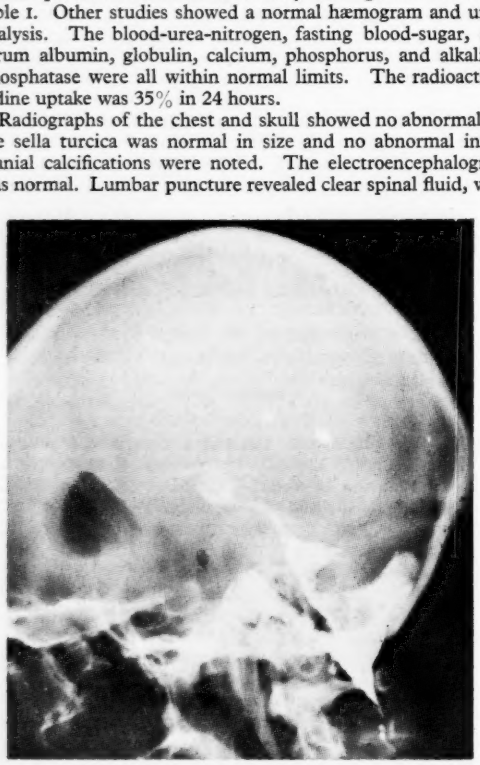


Fig. 1—Case 1: myeloencephalogram, lateral view, with head tilted downward 45° from the horizontal. Note the downward displacement at the junction of the aqueduct and third ventricle.

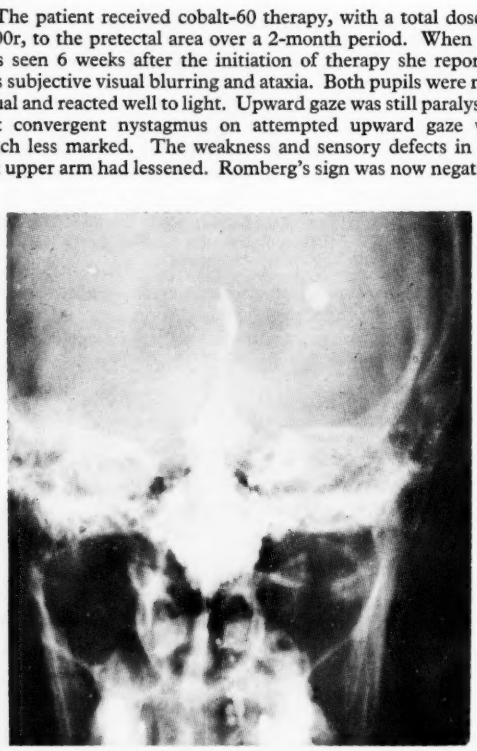


Fig. 2—Case 1: myeloencephalogram, posterior-anterior view, with head as in fig 1. Note the deviation of the inferior part of the third ventricle to the left, and the kink at the junction of the aqueduct and the third ventricle.

THE SECOND CASE

A man of 45, admitted to the Mount Sinai Hospital on May 18, 1960, complained chiefly of weakness of the legs for the past 3 months. 9 months before admission he had had an episode of occipital headache, followed by coma and left hemiparesis which lasted for a week. Upon recovery he had diplopia which persisted for several weeks, and paresis of upward gaze which lasted until he was admitted. 3 months before admission the patient noted the onset of "seizures". These occurred three or four times daily and consisted of weakness of the legs and falling, without loss of consciousness. 2 months previously the patient had been admitted to another hospital where arteriography was said to show a small aneurysm of the left posterior-cerebral artery. After his discharge seizures similar to those described above became increasingly severe. He was treated with primidone ('Mysoline') and benzhexol hydrochloride ('Artane') with striking reduction in the frequency of the seizures. A review of his past medical history was unremarkable. He had no symptoms of gonadal, thyroid, or adrenal dysfunction.

The patient was well developed. His blood-pressure was 115/65 mm. Hg, pulse-rate 74 per minute, and respirations 16 per minute. The skin and hair were of normal texture. The thyroid gland was not palpable. He had a male escutcheon, and the penis and testes were of normal size. The general physical examination revealed no abnormality, and his mental status was normal. The visual fields and fundoscopic examination were normal. Both pupils were regular and reacted slightly to light and well to accommodation. Upward gaze was paralysed bilaterally, and attempted upward gaze produced convergent nystagmus. No nystagmus was noted in any other direction of gaze. Both legs were slightly weak, and Romberg's sign was positive. There was mild finger-nose dystaxia. The deep tendon-reflexes were normal, and Babinski's sign was bilaterally equivocal. Sensory examination was normal. Left carotid compression produced right focal seizures, and right carotid compression produced left focal seizures.

The pertinent chemical laboratory findings are shown in the table. Other studies showed a normal blood picture and urine analysis. The blood-urea-nitrogen, fasting blood-sugar, and the serum albumin, globulin, calcium, and phosphorus were all within normal limits. The water-load test revealed an excretion of 1100 ml. within 5 hours of ingesting 1500 ml. of water. Thyroid studies were not performed because of preceding myelography. The urinary gonadotrophins were positive at 10 mouse uterine units and negative at 50 mouse uterine units.

X-rays of the chest were negative; those of the skull revealed a normal sella turcica, with the calcified pineal in the midline. The electroencephalogram was abnormal, with frontotemporal slow activity strongly accentuated on the right. Lumbar puncture revealed clear fluid, with an initial pressure of 120 mm. water, containing 45 mg. of protein per 100 ml., and 1 lymphocyte per c.mm. Right carotid and vertebral arteriography failed to demonstrate any abnormality. Pneumoencephalography showed a normal fourth ventricle and aqueduct, with no air passing from the aqueduct into the third ventricle. Next day, X-rays of the skull revealed minimal air in the lateral ventricles. Myeloencephalography (fig. 3) confirmed the pneumoencephalographic findings. Ventriculography with a contrast medium (fig. 4) revealed enlarged lateral ventricles and a slightly dilated third ventricle, with no contrast medium passing from the third ventricle into the aqueduct.

The clinical and radiological findings seemed to be most consistent with the presence of a small mass in the area of the rostral aqueduct.

Course

The patient had no seizures throughout his month in the hospital. During this period the weakness of the legs became much less. He was discharged on primidone therapy. When seen as an outpatient 3 months later, the only abnormality was paralysis of upward gaze with retractory nystagmus on attempted upward gaze.

Both patients were shown to have abnormalities in the urinary excretion of aldosterone, though of different kinds (see table). The first patient had subnormal levels of urinary aldosterone on a normal diet, and failed to show the expected rise (Luetscher and Axelrod 1954) in urinary aldosterone after sodium restriction. After radiotherapy, the aldosterone content of the urine was within the normal range, but there still was no rise after sodium deprivation. At this time she improved clinically, but she still had evidence of pretectal area involvement, as manifested by persistence of paresis of upward gaze. The second patient had subnormal levels of urinary aldosterone on a normal

Fig. 3—Case 2: myeloencephalogram, lateral view, with head tilted downward 90° from the horizontal. The contrast medium failed to pass from the rostral aqueduct to the third ventricle.

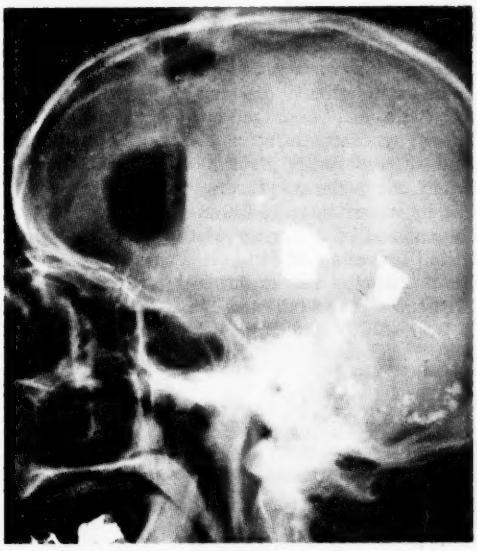


Fig. 4—Case 2: ventriculogram, lateral view, with head horizontal. The contrast medium failed to pass from the posterior inferior third ventricle into the aqueduct. This block to caudal passage is in the same place as the block of the rostral flow of the contrast medium in fig. 3.

diet, but he showed a normal rise after sodium restriction.*

Both patients had abnormal diurnal variations of the plasma-17-hydroxycorticosteroids. This is discussed more fully elsewhere (Krieger 1961). Neither showed clinical or laboratory evidence of endocrinopathy. The serum sodium, chloride, and potassium levels on a routine hospital diet were all within normal limits. Urinary electrolytes were not studied.

Discussion

Farrell's suggestion that the pineal gland is concerned with the regulation of aldosterone secretion is based on the results of ablation, destruction, and replacement studies:

In the dog (Farrell 1960a) a reduction in the adrenal venous aldosterone concentration followed decapitation or decerebration at the mid-collicular level, but did not follow spinal-cord transection or "decortication"; such preparations had normal adrenal venous hydrocortisone concentration. In the cat (Newman et al. 1958) destructive lesions of the ventral diencephalon resulted in a temporary suppression of aldosterone secretion. Further studies (Farrell 1960b) in this species showed that the effective lesion is in the subcomissural area and not necessarily in the pineal body.

Administration of extracts of beef diencephalon (including the pineal), or extracts of pineal alone, brought about an increase in the aldosterone secretory rate in the mid-collicular decerebrate dog (Farrell 1959). Fractionation of these extracts suggested that they might also contain an inhibitor of aldosterone secretion.

Farrell's ablation and destruction experiments (1960a and b) also induced many concomitant physiological changes, and they indicate only grossly the area involved in aldosterone regulation. The results obtained with pineal-replacement studies, however, lend support to the suggestion that the pineal area is involved in the central regulation of aldosterone secretion.

The patients reported in this paper had small pretectal space-occupying lesions demonstrated both clinically and radiologically. These lesions lay just below and caudal to the structures which Farrell implicates in aldosterone regulation. Both patients had low levels of urinary aldosterone. In the first there was in addition a failure to respond to sodium restriction by a rise in urinary excretion of aldosterone. These abnormalities occurred in the absence of clinical and laboratory evidence of pituitary or adrenal disease, or the "cerebral salt-wasting syndrome" described by Peters (1950). (Patients with this syndrome usually had evidence of diffuse cerebral disease rather than localised lesions such as shown in our patients. Peters, however, reported one patient in whom this syndrome appeared 2 days after partial removal of a tumour of the floor of the fourth ventricle [Welt et al. 1952].)

It is noteworthy that in our first case radiotherapy to the pretectal area was followed by partial clinical improvement, and at the same time urinary aldosterone values returned to normal levels, though there was still no rise after sodium restriction.

Hökfelt and Luft (1959) describe a case of an entirely suprasellar meningioma, with normal control levels of urinary aldosterone, but with no rise after sodium restriction; but the extent of the lesion is not mentioned, and we do not know whether the subcomissural or pineal areas were involved. A recent paper (Mosier et al. 1960) describes an 11-year-old boy with an inoperable posterior third-ventricle tumour, who showed sodium wasting and low urinary aldosterone levels after operation. This patient was receiving large amounts of sodium at the time, and this could be responsible for the low urinary aldosterone levels.

Not all investigators (Davis et al. 1959, Ganong et al. 1959) agree with the experimental observations which suggest that the area in the region of the pineal gland is involved in the regulation of aldosterone secretion. The studies on the two patients here reported lend further support to the suggestion that an area in or near the posterior hypothalamus is involved in some aspects of aldosterone regulation.

*Daily urinary excretion of aldosterone may vary appreciably (Hernando et al. 1957). Without repeat determinations on case 2, we cannot say with certainty that the rise after sodium restriction was not within the limits of his normal variation. It remains significant, however, that both patients had subnormal values for urinary aldosterone excretion on their initial examination, and in case 1 these values were remarkably consistent before and after sodium restriction.

Summary

Two patients with small discrete tumours in the pretectal area had subnormal urinary aldosterone levels. One failed to show any rise of urinary aldosterone levels after sodium restriction; the other had a normal response.

One patient improved clinically after radiotherapy and her urinary aldosterone values returned to normal levels, but she still failed to show a rise in urinary aldosterone levels after sodium restriction.

These observations are compared with the experimental findings following lesions involving these areas.

The patients were studied through the courtesy of Dr. M. B. Bender. Pure aldosterone was supplied by Ciba Pharmaceuticals, Summit, New Jersey.

REFERENCES

Davis, J. O., Bahn, R. C., Ball, W. C., Jr. (1959) *Amer. J. Physiol.* **197**, 387.
Farrell, G. (1959) *Endocrinology*, **65**, 29.
— (1960a) *Fed. Proc.* **19**, 601.
— (1960b) *Circulation*, **21**, 1009.
Ganong, W. F., Lieberman, A. H., Daily, W. J. R., Yuen, V. S., Mulrow, P. J., Luetscher, J. A., Jr., Bailey, R. E. (1959) *Endocrinology*, **65**, 18.
Hernando, L., Crabbe, J., Ross, E. J., Reddy, W. J., Renold, A. E., Nelson, D. H., Thorn, G. W. (1957) *Metabolism*, **6**, 518.
Hökfelt, B., Luft, R. (1959) *Acta endocr., Copenhagen*, **32**, 177.
Krieger, D. T. (1961) *J. clin. Endocrin.* **21**, 695.
Luetscher, J. A., Jr., Axelrod, B. J. (1954) *Proc. Soc. exp. Biol., N. Y.* **87**, 650.
Mosier, H. D., Grossman, H. J., Frasier, S. G., Westberg, J. V., Golub, O. J. (1960) *Amer. J. Dis. Child.* **100**, 196.
Neher, R., Wettstein, A. (1956) *J. clin. Invest.* **35**, 800.
Newman, A., Redgate, E. S., Yatsu, F. M., Farrell, G. (1958) *Fed. Proc.* **17**, 1117.
Peters, J. P., Welt, L. G., Sims, A. N., Orloff, J., Needham, J. (1950) *Trans. Ass. Amer. Physcns*, **63**, 57.
Sobel, C., Henry, R., Golub, O. J., Rudy, M. (1959) J. *clin. Endocrin.* **19**, 1302.
Welt, L. G., Seldin, D. W., Nelson, W. P., German, W. J., Peters, J. P. (1952) *Arch. intern. Med.* **90**, 355.

PRESSURISED OXYGEN FOR TOTAL BODY PERFUSION

F. E. WEALE
M.S. Lond., F.R.C.S.
LEVERHULME RESEARCH FELLOW, GUY'S HOSPITAL, LONDON, S.E.1*

THE use of pressurised oxygen to enhance tissue oxygenation has been explored by Boerema et al. (1959) and Smith and Lawson (1958), and its application to a model of a membrane oxygenator has been investigated in Dagher's (1959) in-vitro studies. Physical solution of oxygen in plasma can be increased upon pressurisation, before its combination with oxyhæmoglobin, by a factor of 15 (Illingworth 1960).

Enhanced solution of oxygen in blood may become important because bigger patients are being submitted to open cardiac surgery, and because the increasing number of patients coming to operation will require of

*Present address: Surgical Professorial Unit, St. Bartholomew's Hospital, London, E.C.1.

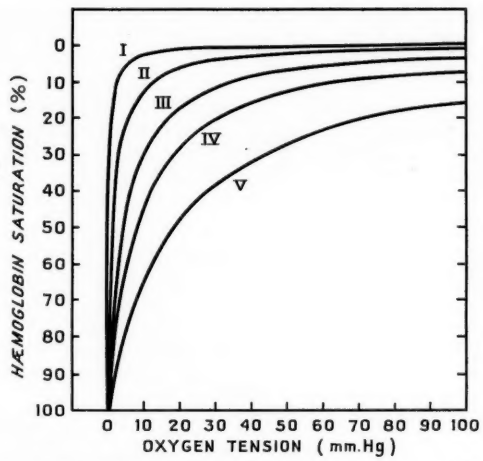


Fig. 1—Oxygen-dissociation curves of blood at different temperatures (from Barcroft and Hill 1910).

Dissociation curves I, II, III, IV, and V correspond to 16°, 25°, 32°, 38°, and 49°C respectively.

heart-lung machines as high an oxygenation-capacity/priming-volume ratio as possible, to relieve the transfusion services of some of the increasing pressure on them. By priming volume is meant the volume of blood needed to fill a heart-lung machine, and this tends to increase in models designed for bigger patients.

Another method for achieving these desirable results was suggested by the studies of Barcroft and Hill (1910), who found that the oxygen-dissociation curve of blood shifted to the left upon cooling (fig. 1).

Pilot experiments were therefore designed to test the practicability of: (*a*) pressurising blood with oxygen in an oxygenator; (*b*) pre-cooling the blood. To some extent this problem has already been solved by the hypothermic bypass.

Apparatus

The construction of a simple pressure-chamber was guided by an arbitrary limit to pressurisation of three atmospheres of oxygen absolute.

The heart-lung machine model used is shown diagrammatically in fig. 2. The circuit has been arrived at after some considerable experimentation designed to minimise the largely theoretical objections to bubble formation voiced by Ito et al. (1958). Urschel et al. (1960) have already stated that bubble formation resulting from the warming of cold blood in the course of bypass appeared to them unlikely.

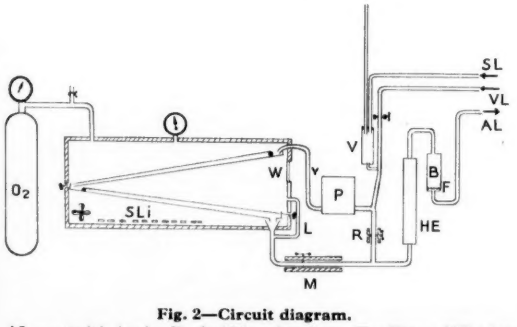


Fig. 2—Circuit diagram.

AL=arterial lead; B=bubble chamber; F=filter; HE=heat exchanger; L=level indicator; M=main clamp; P=monopump; R=recirculation loop and clamp; SL=suction lead; SLi=soda lime; V=venous reservoir; VL=venous lead; W=perspex window; Y=lead into pressure-chamber.

The oxygenator essentially consists of two perspex trays over which a film of blood is spread giving an oxygenation area not exceeding 0·4 sq. m. The blood, on entering the oxygenator through the two limbs of the Y-lead (fig. 2), is partly dammed back and spread out by the wiper lying loosely on the upper perspex plate (fig. 3). A film of blood is obtained by withdrawing this wiper slowly before bypass. A long handle provided for this purpose projects through a hole in the wall of the oxygenator which can be hermetically sealed. On leaving the upper tray the blood drops on to the lower one, which is served by a similar wiper, and which is equally supported during bypass by small wedges about $^1/_{32}$ in. high, thus allowing blood to pass underneath. The long clamp, (fig. 2, M), designed to make the inevitable pressure-gradient less steep, diminishes the pressure of blood from that inside the chamber to more suitable perfusion levels. The heat-exchanger, bubbletrap, and filter are self-explanatory. Soda-lime was scattered over the floor of the chamber, and the oxygen within it agitated by a non-sparking fan motor.

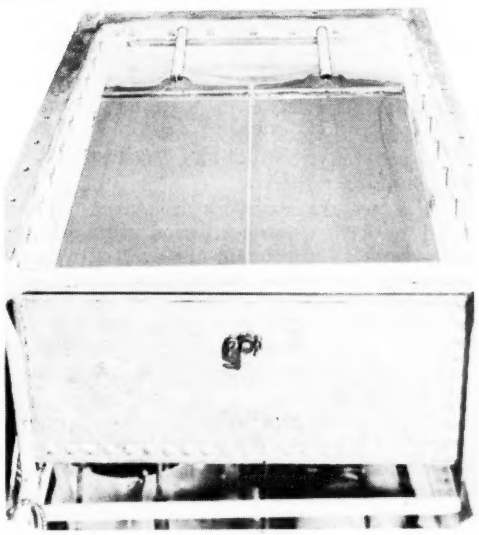


Fig. 3—Oxygenator with lid removed to show flow of blood over upper perspex tray.

The blood-wiper is near the upper end of the tray, supported on two wedges to allow the blood to flow underneath it.

Method and Materials

The circuit is primed with filtered heparinised blood; and, when all air has been expelled, the blood is made to circulate slowly via the recirculation loop. By tightening the main clamp a steady level of blood is maintained in the level indicator. The chamber is washed out with oxygen to remove all its atmospheric nitrogen. When the arterial and venous leads are connected to the animal the pressure in the chamber is raised to five lb. per sq. in., to lift the blood to operating-table level and to overcome arterial pressure. This requires a further tightening of the main clamp to prevent too rapid an efflux of blood from the chamber. Partial bypass is started by graded release of the adjustable clamp on the venous lead, occlusion of the recirculation loop, and opening the arterial line.

Pump speed is adjusted according to the venous return, which is at all times apparent in the venous reservoir. The degree of occlusion required of the main clamp is dictated by the level of blood in the level indicator. This needs close watching: with too low a level there is a risk of oxygen embolism, while with too high a level blood may overflow on

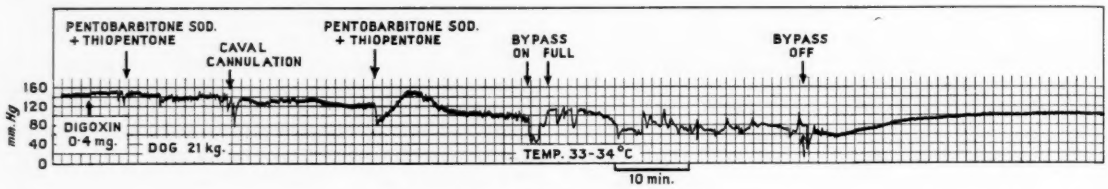


Fig. 4—A typical blood-pressure tracing.

to the bottom of the oxygen chamber. Once equilibrium has been obtained, it is possible to raise the oxygen pressure to the desired level within a few minutes, and equally to change to full bypass. Hypothermia can be used, if needed, by cooling the blood in the heat exchanger.

In our experiments we have recorded both arterial and venous pressure from the femoral vessels. To dispense with either deprives one of valuable information; recording venous pressure in particular has been of great value at the end of bypass when heart take-over is tested for.

Forty experiments were carried out on dogs of several breeds, including 30 kg. greyhounds. Survivals were attempted in some of these, but in no case did survival extend beyond the morning of the following day.

Results

Pressurisation

Fig. 4 shows a typical blood-pressure tracing during operation and the return of the blood-pressure after bypass to a satisfactory level.

Fig. 5 shows the variations in oxygen saturation, measured by a Kipp hæmoreflector, with changes in oxygen pressure. The generally low levels of oxygenation are related to the inadequate oxygenation area of our model, but they focus attention on the fact that a rise in pressure will lead to an increase in arterial oxygenation. As would be expected, recirculation of the blood is an additional factor leading to improved oxygenation (second tracing). Some of the initial venous readings are rather higher than expected; this is because we always withdrew our first venous samples before the arterial ones at the commencement of bypass, and it takes some time before even the venous-blood oxygenation falls to the level appropriate to the low arterial-blood oxygenation.

These low oxygenation levels are consistent with the small maximum oxygenation surface of 0·4 sq. m. The influence of oxygen-pressure variations is more easily demonstrable at hypoxic levels. There is no basic difficulty in applying pressurised oxygen to heart-lung machines currently in use, and we have placed a rotating disc oxygenator into our pressure chamber with success.

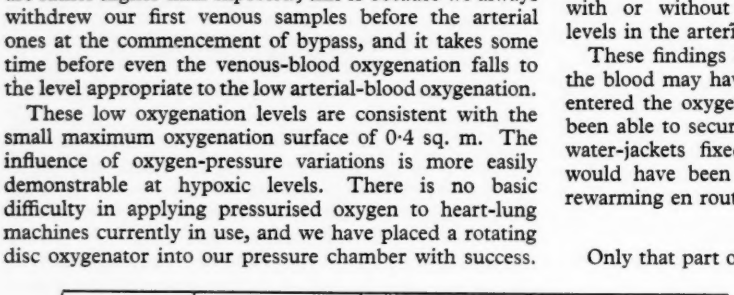


Fig. 5—Variations of arterial and venous blood-oxygen saturations with variations in chamber oxygen pressure.
Samples taken after minimum of 4-minute equilibration.

Marx et all. (1960), in a theoretical study of the relation of blood turbulence to oxygenation emphasise how much is to be gained by good mixing, (also shown by fig. 5, second tracing), and this is what only rotating discs can achieve. To avoid dangers from sparking it is essential to use induction motors to rotate the spindle which supports the discs.

At no time did we observe bubbles of any size in our bubble chamber, even though this was separated by about four feet of tubing from the main clamp and there was therefore time for bubble separation. A safety factor may have been provided by the generally low arterial oxygenation levels, so that any molecular oxygen freed from physical solution would immediately be mopped up by the unsaturated hæmoglobin. This type of machine should never be allowed to achieve 100% oxygenation in the main chamber.

Precooling

Fig. 1 shows that something like a 10°C fall in the temperature of the hæmoglobin is necessary in order materially to increase the blood-oxygen content.

We achieved a drop of something like 12–13°C in the venous reservoir by interpolating a heat exchanger in the venous line, and maintained the animal at its original temperature by running the customary heat-exchanger a little hotter.

In effect, with this experimental set-up we were unable to demonstrate what we had set out to do. Oxygenation with or without precooling yielded identical oxygen levels in the arterial line.

These findings are not necessarily conclusive, because the blood may have sufficiently rewarmed by the time it entered the oxygenator to obscure any benefit. Had we been able to secure oxygenator trays made of metal with water-jackets fixed to their undersurface, the cooling would have been more effective, and all possibility of rewarming en route would have been excluded.

Discussion

Only that part of our study concerned with pressurised oxygen has yielded positive results. When a heart-lung machine is designed, one object is to provide the largest possible oxygenation surface for a given priming volume. But there are limits beyond which careful exploitation of the dimensions available cannot go. The combined use of bypass and hypothermia is one way in which a heavier animal can have its life supported where either method used in isolation might be insufficient. Pressurisation of oxygen as described here appears to provide another weapon which might help to improve oxygenation capacity when other means are exhausted.

Cumbersome, and perhaps dangerous, methods involving pressurisation of both patient and operating team are unlikely to be accepted if the same principle can be equally well applied more adroitly. The ready response of arterial oxygen saturation changes with changes in chamber pressure indicates a promising line of advance. Further work—especially an investigation into the amount of hæmolysis produced by this method, and a more precise quantitative assessment of its advantages—is now required.

Summary

A method is outlined by which pressurised oxygen is used for the oxygenation of blood in a heart-lung machine.

I am indebted to Sir Russell Brock for his encouragement and Mr. D. Phelan and Mrs. E. Stevens for technical assistance. Fig. 1 is reproduced from the *Journal of Physiology* by permission of the editors.

REFERENCES

Barcroft, J., Hill, A. V. (1910) *J. Physiol.* **39,** 411.
Boerema, I., Meyne, N. G., Brummelkamp, W. H., Bouma, S., Mensch, M. H., Kamermans, F., Hanf, M. S., Aalderen, W. (1959) *Arch. chir. neerl.* **11,** 70.
Dagher, I. K. (1959) *J. thorac. Surg.* **37,** 100.
Ito, I., Kolff, W. J., Effler, D. B. (1958) *Clev. clin. Quart.* **25,** 9.
Illingworth, C. F. W. (1960) Personal communication.
Marx, T. I., Snyder, W. E., Andrew, D. St. J., Moeller, C. E. (1960) *J. appl. Physiol.* (1960) **15,** 1123.
Smith, G., Lawson, D. A. (1958) *Scot. med. J.* **3,** 346.
Urschel, H. C., Greenberg, J. J., Roth, E. J. (1960) *J. thorac. cardiovasc. Surg.* **39,** 318.

SUSTAINED EXTERNAL MANUAL SYSTOLE DURING VENTRICULAR FIBRILLATION

ROBERT E. FUISZ M.D. MARK G. PERLROTH M.D.
INTERNS IN MEDICINE

ELI A. FRIEDMAN M.D.
SENIOR ASSISTANT RESIDENT IN MEDICINE

HOUSE STAFF, HARVARD UNIVERSITY MEDICAL SERVICE OF PETER BENT BRIGHAM HOSPITAL, BOSTON, MASSACHUSETTS

EUGENE C. EPPINGER M.D.
ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; PHYSICIAN, PETER BENT BRIGHAM HOSPITAL

DESPITE many recent advances in the prevention and control of cardiac arrhythmias, ventricular fibrillation has hitherto almost invariably presaged death. The early experimental work of Hooker (Hooker 1929, Hooker et al. 1933) and Wiggers (1936, 1940) in animals indicated that the mammalian ventricle could be effectively revived from fibrillation by electroshock, and with the dawn of cardiac surgery this has become a commonplace event. The report by Beck et al. (1956) was followed by repeated examples of effective defibrillation after emergency thoracotomy in patients developing this arrhythmia when they were not in the operating-room. However, the difficulties attending this procedure rapidly became evident: they often included a combination of bleeding, cardiac laceration, lack of trained personnel, and inability to maintain ventilation owing to pneumothorax.

The demonstration by Kouwenhoven et al. (1960) that external manual systole could frequently accomplish adequate perfusion of the systemic and pulmonary vessels in a period of ventricular arrest or fibrillation has opened a new approach to the treatment of these arrhythmias. We describe here our experience with a patient in whom ventricular fibrillation was successfully terminated after forty-five minutes of continuous external cardiac massage.

Case-report

A 61-year-old businessman was admitted to the Peter Bent Brigham Hospital medical service for the sixth time with a complaint of precordial palpitations and substernal chest pain of approximately ten hours' duration. The patient was known to have labile hypertension of thirty-five years' duration with gradually progressive intermittent claudication and angina pectoris during the previous ten years. Transient left hemiparesis had followed right carotid sinus compression for paroxysmal atrial tachycardia nine years before admission. Six weeks previously he had been admitted to this hospital with acute myocardial infarction complicated by shock and pulmonary œdema. An intravenous digitalis preparation promptly restored cardiac compensation and blood-pressure at that time. After a brief episode of spontaneous atrial flutter during the first week after his myocardial infarction the patient's condition was stabilised, and thereafter he recovered uneventfully and was discharged on the thirty-third hospital day. He was placed on maintenance digoxin (0·25 mg. orally per day) and long-term anticoagulant prophylaxis.

Examination

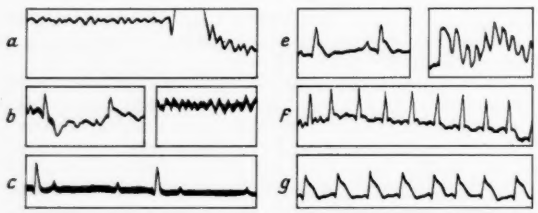
On admission the patient was pale and appeared older than his stated age; he complained bitterly of substernal chest pain. The vital signs were as follows: blood-pressure 152/110 mm. Hg; pulse-rate 145–150 per minute, regular; respirations 22 per minute; and temperature 98·6°F orally.

Examination of the fundi showed bilateral retinal arteriolar narrowing with areas of arteriovenous compression. The carotid pulsations were diminished bilaterally without an audible bruit. The chest was slightly emphysematous but clear to percussion and auscultation. A hyperactive precordium with the maximum apical impulse in the left fifth intercostal space outside the midclavicular line was noted. The cardiac sounds were of good tonal quality with a loud, snapping second heart sound in the aortic area. A grade 2/6 early systolic ejection murmur was audible at the cardiac base, and the first heart sound varied in intensity at the cardiac apex. An early ventricular diastolic filling sound was audible along the left sternal border. The jugular venous system was not distended at 90°. The abdomen was scaphoid, and no organ was palpably enlarged. The legs were cold and showed trophic changes, pendant rubor, and absent pulsations below the femoral vessels bilaterally.

The hæmogram and urinalysis were normal on admission. The blood-urea-nitrogen was 23 mg. per 100 ml., and the serum-electrolytes were as follows: sodium 140 mEq. per litre; potassium 4·4 mEq. per litre, repeat 4·5 mEq. per litre; chloride 108 mEq. per litre; carbon dioxide 28·6 mEq. per litre. The lactic dehydrogenase was 136 Wacker units (normal less than 140). The prothrombin was 14·5% of normal, and a stool specimen was positive for occult blood. An electrocardiogram at this time defined the tachycardia as atrial flutter with a 2 : 1 ventricular response and a cardiac rate of 145 per minute.

Course

In view of previous experience with this patient it was elected to begin the intravenous administration of ouabain in doses of 0·1 mg. every thirty minutes with continual electrocardiographic monitoring. After 0·5 mg. had been administered in this manner the patient complained of nausea; and although no discernable ventricular slowing was evident, it was decided to begin a period of observation in order to ascertain the maximum effect of this rapid-acting glycoside without precipitating overt drug intoxication. After a three-hour interval an additional 0·1 mg. of ouabain was administered, but prompt return of nausea precluded further digitalisation. At this point the patient was clearly deteriorating with the development of moist râles in both lung bases, increasing dyspnœa, and persistent precordial pain only partly relieved by narcotic agents. At exactly two hours and fifteen minutes after the last dose of ouabain the patient suddenly became unresponsive and apnœic and exhibited clonic movements of the upper extremities. There was no discernible pulse, and the pre-



Tracings represent selected strips taken during the period of cardiac resuscitation. All are standard lead II.

a. Ventricular fibrillation. This pattern was present throughout the forty-five-minute period of resuscitation.

b. Tracing represents response to the first 550-volt countershock and depicts rapid return of ventricular fibrillation.

c. Response to second 550-volt countershock with evolution of complete auriculoventricular dissociation and nodal pacemaker. Prolonged QRS probably represents intraventricular block secondary to antecedent hypoxia.

d. Tracing showing development of multifocal ventricular tachycardia with transition to ventricular fibrillation.

e. Third successful countershock showing first-degree heart-block with intraventricular conduction delay. Rapid return of ventricular fibrillation is shown in the second portion of the tracing.

f. Strip showing nodal rhythm after transient run of sinus tachycardia following fourth 550-volt countershock.

g. Development of incomplete auriculoventricular dissocation with nodal pacemaker and marked ST segment elevation.

h. Shows return to sinus rhythm with a single aberrantly conducted beat. This tracing was taken four hours after the first application of countershock.

---

cordium was silent. The electrocardiogram showed ventricular fibrillation (see figure, *a*).

Immediate external manual systole was begun with rhythmic compression at the lower left sternum, using the thenar and hypothenar eminences of the hand at a rate of 60–70 per minute. The patient remained totally unresponsive, but pulsations could be felt in the carotid, radial, and femoral arteries coincident with each external massage. The pupillary diameter almost immediately returned to normal. After fleeting attempts to maintain respiratory exchange with the Kreislman respirator had proved futile, rapid endotracheal intubation was completed by Dr. George Hill and bag breathing initiated. At no time after the onset of massage was the patient noted to be cyanotic. Since the closed-chest A.C. defibrillator was being held in readiness for a patient elsewhere in the hospital, an unavoidable delay was incurred. Consequently it was elected to monitor the rate of external massage by observing pupillary diameter and the peripheral pulsations. Unfortunately no blood-pressure readings were taken.

After forty-five minutes of continuous external massage and assisted respirations the pupils remained small and reacted to light briskly and equally. Successive electroshocks with the closed chest A.C. defibrillator at 250 volts, 350 volts, and 450 volts failed to end the pattern of ventricular fibrillation. After each shock external cardiac massage was reinstituted, utilising pupillary diameter as an end-point, both to maintain cerebral blood-flow and to gain the potentiating action of myocardial oxygenation on the succeeding countershock (Wiggers 1936). After a 550-volt shock complete auriculo-ventricular dissociation with a nodal or high bundle pacemaker at a rate of 30 per minute evolved spontaneously. Isoproterenol hydrochloride (0·1 mg.) was administered intravenously, and the nodal pacemaker gradually increased in rate with sudden re-emergence of ventricular fibrillation. A second 550-volt countershock reinstituted a nodal pacemaker which rapidly increased in rate over the next minute and then evolved successively into multifocal ventricular tachycardia and ventricular fibrillation. Countershock for the third time with 550 volts resulted in a transient slow sinus rhythm with first-degree heart-block and rapid return of ventricular fibrillation. A fourth 550-volt shock re-established a fleeting period of sinus rhythm with the subsequent emergence of a series of bizarre supraventricular arrhythmias (see figure A), culminating in a normal sinus pacemaker four hours after external cardiac massage was begun.

Within twenty minutes of the last countershock the patient was noted to respond to commands, and spontaneous respirations at the rate of 20 per minute were counted. Blood-pressure was maintained at 110 mm. Hg systolic with an intravenous drip of 50 mg. metaraminol bitartrate in 1 litre of 5% dextrose in water. On physical examination at this time there were bibasilar râles, a slight left-sided facial and extremity weakness, and exquisite tenderness over the entire precordium with voluntary " splinting " of respirations bilaterally. The patient subsequently vomited and aspiration was thought to occur, since coughing was much limited by the thoracic trauma incurred during external massage.

During the next seventy-two hours the patient was tapered off pressor drugs, but pneumonitis developed in the right middle lobe. Radiographic examination of the chest confirmed a patchy infiltrate in the right mid-lung field, but no rib fractures were seen. Urine output was at no time impaired, and, except for a rise in lactic dehydrogenase to 696 Wacker units, blood-chemistry determinations remained normal. The left hemiparesis cleared in thirty-six hours without residua, and the electrocardiogram remained stable. Therapy with penicillin and chloramphenicol induced rapid clearing of the pulmonary infiltrate and return of temperature to normal. The patient was placed on maintenance digoxin (0·25 mg. daily) and walked from bed to chair beginning on the sixth day after external manual systole. Ten days after the resuscitation he sustained a sudden transverse myelitis with paraplegia, bladder paralysis, and absent sensory modalities below the distribution of the 8th spinal segment. This was followed by the development of a diffuse herpetic lesion extending over the thighs and buttocks. Although the possibility of a primary herpes myelitis was considered, it was thought more likely that this represented a vascular lesion of the spinal cord secondary to diffuse arteriosclerotic disease. The onset ten days after cardiac resuscitation made it improbable that these two events were causally related. The patient's cardiac status subsequently remained stable, although paraplegia and bladder paralysis persisted.

On the morning of the forty-ninth hospital day, just prior to contemplated discharge, the patient died suddenly. Necropsy revealed extensive multifocal areas of old and recent myocardial necrosis with severe diffuse coronary-artery disease. No obvious sequelæ attributable to external cardiac massage were demonstrable.

Discussion

The efficacy of external cardiac massage in maintaining a rate of perfusion sufficient for basal requirements was put to a severe test in this patient. Advanced arteriosclerotic cardiovascular disease with cerebral, peripheral, and coronary manifestations precluded any attempt at open thoracotomy. Despite a severely compromised vascular system, continuous perfusion was adequately maintained for a full forty-five minutes without neurological, renal, or peripheral sequelæ. The fact that adequate coronary blood-flow was being maintained is best attested by the response to electroshock, since defibrillation by this method is notoriously ineffective when applied to anoxic cardiac muscle. The elevation of lactic dehydrogenase was compatible with cardiac necrosis but could reflect direct myocardial or skeletal-muscle trauma incurred during resuscitation in addition to frank myocardial infarction. Although femoral, radial, and carotid pulsations could be felt with external cardiac massage, the efficiency of perfusion was monitored best by observation of pupillary diameter. As the rate of compression fell below an

optimum the pupils dilated rapidly; and they reverted to normal almost immediately as the frequency of massage was increased. We also gained the impression that the mechanical movement of the thorax associated with sternal compression provided adequate pulmonary ventilation for at least the ten minutes before endotracheal intubation. Attempts to utilise the Kreislman respirator during this period were largely ineffectual, since it was impossible to synchronise the instrument with the external massage.

The suggestion that rib fracture may be an unavoidable complication of effective external cardiac massage was not borne out in this patient. Vomiting may attend unavoidable compression of the stomach; and endotracheal intubation gives some protection against aspiration of vomitus besides ensuring an adequate airway. In retrospect we should probably have been less hasty in removing the endotracheal tube in this patient since an aspiration pneumonitis might conceivably have been averted. Trauma to the thoracic wall and costosternal articulations is an unavoidable sequel of prolonged massage and results in much limitation of respiratory excursions similar to that in a patient after thoracotomy. Consequently breathing exercises and forced coughing are probably indicated to prevent pulmonary collapse, obstruction, and infection in the immediate post-massage period. Since a significant number of patients in whom external manual systole is utilised will be receiving anticoagulants, the theoretical possibility of hæmorrhagic pericardial effusion secondary to direct trauma should be considered. At present we are not aware of any data in this regard.

In the first published report of extensive experience with this technique Kouwenhoven et al. (1960) reported twenty successful resuscitations in twenty attempts, with ultimate survival in fourteen patients. Three of these were in ventricular fibrillation, and successful defibrillation with the closed-chest A.C. defibrillator was accomplished. In one of the patients cardiac massage was maintained for twenty minutes while defibrillation equipment was being brought to the scene. These same investigators reported systolic blood-pressures of 60–100 mm. Hg with this technique in man. In a group of thirteen collected cases commented on by Barringer (1961), three patients with ventricular fibrillation were resuscitated successfully until controlled thoracotomy and internal defibrillation could be initiated. One of these reverted to normal sinus rhythm while the remaining two died—one of ventricular laceration, and the other of inability to maintain cardiac contraction. Thus, exclusive of the present case, at least six patients with cardiac arrest due to ventricular fibrillation have been reported in which the Kouwenhoven procedure was applied; and four patients survived. Three were treated by closed-chest defibrillation and one with eventual thoracotomy and internal defibrillation.

If continued experience with external cardiac massage sustains the impression that this procedure can maintain adequate basal perfusion of the pulmonary and systemic vasculature, the advantages of the method will be multifold. When cardiac arrest is diagnosed, the observer should begin immediate external massage at the rate of 60–70 per minute utilising pupillary diameter and the peripheral or carotid pulsations as indices of response. An adequate airway should be maintained and mouth-to-mouth breathing instituted until rapid endotracheal intubation can be effected. During this interval electrocardiographic monitoring should clarify the diagnosis of cardiac arrest, idioventricular rhythm with inadequate cardiac output, or ventricular fibrillation. The appropriate pharmacological or physical methods for counteracting these arrhythmias may then be instituted according to the facilities at hand.

In a general medical ward arteriosclerotic heart-disease and myocardial infarction account for the vast majority of sudden, unexpected deaths. Undoubtedly many of these patients would survive for some time but for the development of arrhythmia in a heart temporarily embarrassed by anoxia and injury. This simple resuscitative technique, requiring a minimum of personnel, equipment, and advance preparation, should measurably increase the number of patients to whom support during this critical interval can be extended.

Summary

Successful termination of ventricular fibrillation by repeated closed-chest electroshock after forty-five minutes of continuous external manual systole is reported.

REFERENCES

Beck, C. S., Weckesser, E. C., Berry, F. M. (1956) *J. Amer. med. Ass.* **161**, 434.
Friedlich, A., Barringer, R., and others. (1961) *Amer. Practit.* **12**, 128.
Hooker, D. R. (1929) *Amer. J. Physiol.* **91**, 305.
— Kouwenhoven, W. B., Langworthy, O. R. (1933) *ibid.* **103**, 444.
Kouwenhoven, W. B., Jude, J. R., Knickerbocker, G. G. (1960) *J. Amer. med. Ass.* **173**, 1064.
Wiggers, C. J. (1936) *Amer. J. Physiol.* **116**, 161.
— (1940) *Amer. Heart J.* **20**, 413.

Addendum

Since this manuscript was submitted a report has been published describing further experience with external manual systole in ventricular fibrillation. The complications associated with the use of this procedure in 84 patients are described in detail (R. J. Baringer, E. W. Salzman, W. A. Jones, A. L. Friedlich. *New Engl. J. Med.* 1961, **265**, 62).

"DROP ATTACKS" IN CYANOTIC CONGENITAL HEART-DISEASE

D. W. EVANS
M.B. Wales, M.R.C.P., D.C.H.
SENIOR MEDICAL REGISTRAR

O. BRENNER
M.D. Birm., F.R.C.P.
CONSULTANT PHYSICIAN

QUEEN ELIZABETH HOSPITAL, BIRMINGHAM

THE various neurological manifestations associated with congenital heart-disease have often aroused interest. These include epileptiform attacks (Brown 1950, Kjellberg et al. 1955, Tyler and Clark 1958), or mere "stiffening" without loss of consciousness (Tyler and Clark 1957), and diverse cerebral symptoms (White 1951). Also, cyanotic patients are liable to a peculiar form of "drop attack" which seems never to have been described. To illustrate this symptom-complex, we shall report briefly three cases currently under observation. It consists of recurrent falls while walking, with very rapid recovery of power in the legs, and no disturbance of consciousness. Sometimes paræsthesiæ in the legs immediately precede the fall, and sometimes the legs do not feel quite normal for a minute or two afterwards. The attacks seem to be precipitated by very variable amounts of exercise, and they tend to recur frequently for a few weeks or months, and then to disappear.

Case-reports

THE FIRST CASE

Cor Triloculare

A woman of 26, blue from birth and short of breath on exertion for as long as she can remember, experienced drop attacks four years ago. The first attack occurred during her daily walk to work—a distance of rather less than a mile which she had covered regularly, without stopping en route, for five years. Suddenly, and without any warning, her legs gave way and she fell. There was no faintness or loss of consciousness, and she was able to rise within a few seconds and continue her walk. Further attacks followed with increasing frequency during the next twelve months, towards the end of which she experienced them nearly every day—sometimes after walking half a mile, and sometimes after taking only a few steps. Occasionally she had a few seconds' warning of the impending fall, in that she was aware of slight shaking of the legs and a feeling that they were " turning to rubber ". Very rarely did the warning enable her to avert the attack by stopping or resting. She sometimes needed help to regain her feet after falling, but once erect she could resume her walk without further delay.

During these twelve months she was also liable to short attacks of tight chest pain, radiating into the left arm and down to the hand, which were provoked by exertion and rapidly eased by rest.

A year after the attacks started she was treated for " iron-deficiency anæmia " (hæmoglobin 13 g. per 100 ml. and packed-cell volume (P.C.V.) 50%, as compared with her usual levels of 20·9 g. and 74% respectively). She quickly regained her natural polycythæmic state, and she has had no drop attacks or angina since. She has never squatted.

There is no family history of epilepsy, and her central nervous system has always been normal on clinical examination. X-rays of the skull are normal. An electroencephalogram (E.E.G.) showed quite numerous brief irregularities, commonly in the shape of little runs of rhythmic waves at 20 cycles per second, or mixed sharp-wave and theta events.

The diagnosis of cor triloculare biventriculare, with pulmonary stenosis and ventricular septal defect, was made by cardiac catheterisation and confirmed at thoracotomy.

THE SECOND CASE

Tetralogy of Fallot

A 16-year-old girl, blue since infancy and too short of breath ever to play games, had in the three months before her most recent hospital admission experienced gripping retrosternal pain on exertion, relieved in five or ten minutes by resting or more rapidly by chewing tablets of glyceryl trinitrate. Also during these three months she had had drop attacks in which the legs folded up under her while walking. Consciousness was not lost, and she was always able to rise immediately, but she usually had to stand still for a minute or two before walking on. These attacks were often preceded by numbness in the legs, from the hips downwards, of several minutes' duration. Such prolonged warning had often allowed her to reach a seat or some support before falling.

While in hospital (primarily for confirmation of the diagnosis of Fallot's tetralogy by cardiac catheterisation) she was found to be relatively anæmic, with Hb 12·5 g. per 100 ml., P.C.V. 47%, and serum-iron 36 μg. per 100 ml. Excessive menstrual loss was thought to account for the iron deficiency, and after iron therapy her Hb rose to 20·2 g. per 100 ml. She has had no further attacks of falling to date. She has never squatted to relieve breathlessness.

She has no family history of epilepsy, and no clinical abnormality in her central nervous system. Skull X-rays are normal. An E.E.G. showed persistent diffuse slow-wave background, with one or two more clearly paroxysmal interruptions of brief duration.

THE THIRD CASE

Tricuspid Atresia with Truncus Artĕriosus and Dextrocardia

A boy of 10, blue from birth but still able to run and play without acute distress, first fell whilst walking about three months before a recent stay in hospital. His legs suddenly gave way under him after he had covered a mile at a steady pace; he was able to get up immediately but he could not walk on again for a few seconds because the legs felt stiff. Similar attacks occurred about twenty times during the next two months, sometimes after he had taken only a few steps and sometimes after about a mile. There was never any disturbance of consciousness, and no paræsthesiæ to warn him of the coming fall. He was not anæmic or generally unwell during this period, and he has had no further attacks. There is no history of squatting.

Angiocardiography revealed the presence of a truncus arteriosus as well as tricuspid atresia. There is dextrocardia without complete situs inversus. His Hb is 17·7 g. per 100 ml., with P.C.V. 56% and a normal film.

His family has no history of epilepsy, and his central nervous system is clinically normal. Skull X-rays are normal except for poor development of the paranasal sinuses. An E.E.G. was generally unstable, with quite frequent passages of slow theta waves, tending to show paroxysmal marshalling.

Discussion

The patients' descriptions of their drop attacks are remarkably consistent. The onset is typically sudden (though there may be some warning paræsthesiæ in the legs), and the period of uselessness of the legs is very short. Commonly the legs feel abnormal in one way or another for about a minute after the fall, and then full power and control are regained. Attacks seem to occur only during exercise, but they are not regularly precipitated by any particular degree of exertion. Dyspnœa and angina do not tend to occur at the same time, and there is no association with squatting. Consciousness is unimpaired, and no rigidity, clonic movements, or sphincter disturbances are reported. None of the three cases described above had an epileptic background, although E.E.G. abnormalities were found in each case.

These falling attacks may be of similar nature to " akinetic " epilepsy (Brain 1955). They bear a striking resemblance to the drop attacks of middle and old age (Kremer 1958, Sheldon 1960) which have been attributed to a failure, at brain-stem level, of the postural-tone control system. Vascular occlusion is unlikely to be the underlying cause in our cases, but perhaps an increase during exercise in the degree of anoxæmia acts in some way as a trigger mechanism. The fact that attacks occurred in two patients only when they were relatively anæmic may be significant.

It seems improbable that any local circulatory disturbance in the legs could cause such a sudden bilateral loss of muscle tone, although it might be responsible for the paræsthesiæ.

Summary

Recurrent attacks of falling during walking may occur in patients with cyanotic congenital heart-disease. Three such cases are briefly described.

We are indebted to Dr. Michael Jefferson for kindly reporting on the E.E.Gs.

REFERENCES

Brain, R. (1955) Diseases of the Nervous System; p. 903. London.
Brown, J. W. (1950) Congenital Heart Disease; p. 300. London.
Kjellberg. S. R., Mannheimer, E., Rudhe, U., Jonsson, B. (1955) Diagnosis of Congenital Heart Disease; p. 186. Chicago.
Kremer, M. (1958) *Brit. med. J.* ii, 121.
Sheldon, J. H. (1960) *ibid.* ii, 1685.
Tyler, H. R., Clark, D. B. (1957) *A.M.A. Arch. Neurol. Psychiat.* **77**, 17.
— — (1958) *ibid.* **79**, 506.
White, P. D. (1951) Heart Disease; p. 296. New York.

TUBERCULOUS ADDISON'S DISEASE

A CASE APPARENTLY CURED BY CHEMOTHERAPY

T. D. ANNEAR
M.B. Lond.
FORMER MEDICAL REGISTRAR

G. P. BAKER
M.D. Cantab., M.R.C.P.
CONSULTANT PHYSICIAN, MAYDAY HOSPITAL, CROYDON, SURREY

ADDISON'S disease (chronic suprarenal cortical insufficiency) is generally regarded as incurable in the sense that substitution therapy is required for the rest of the patient's life, as in diabetes mellitus. Spontaneous recovery is said to be very rare (Simpson 1956). The majority of cases are due either to tuberculous infection of the suprarenals or to atrophy of unknown cause; and, even in cases which are tuberculous, signs of infection (apart from tuberculosis in other organs) are usually very slight or absent. Though pyrexia does appear at times, especially during crises, it is uncommon; the temperature is usually subnormal (Simpson 1959, Spence 1953).

The case reported below is unusual in that the infection was very " active ", and the patient had striking fever with a continuous irregular pyrexia up to 102·8°F, which was observed while he was an inpatient for four weeks; yet within five days of beginning treatment with streptomycin and isoniazid his temperature fell to normal and remained so. No evidence of tuberculosis in any other organ was found. Moreover, although the patient required salt by mouth and deoxycortone to maintain his plasma-sodium level and blood-pressure, by the end of five months' chemotherapy both were discontinued, and the plasma-electrolytes and blood-pressure have since remained normal without any further treatment.

Case-report

A slightly built gardener, aged 58, was first seen as an outpatient in September, 1954, complaining of malaise, loss of weight, vague aches and pains, and " lumps under the skin ". The only abnormal findings at this time were mild left-sided epididymo-orchitis, slight albuminuria, and a raised erythrocyte-sedimentation rate (E.S.R.) of 27 mm. in one hour (Westergren). The blood-pressure was 140/100 mm. Hg, and the hæmoglobin was 93% (13·7 g. per 100 ml.). No subcutaneous lumps were felt and no skin pigmentation was recorded. The epididymo-orchitis subsided completely in a few weeks, no definite diagnosis being made at that time.

He was not seen again until June, 1956, when he complained of progressive weakness, discomfort in the abdomen and chest, further loss of weight, and a recent pyrexial attack for which he had received penicillin from his own doctor. He now had generalised pigmentation particularly on the exposed areas of the skin, which was very suggestive of Addison's disease, but no pigmentation was seen in his mouth. He was thin (weight 8 st. 2 lb.), and he had lost 10 lb. since 1954. His blood-pressure had fallen to 115/75 and the urine contained a trace of albumin. No other abnormality was found. The testes and epididymes were normal. The plasma contained sodium 133, potassium 4·9, and chloride 96 mEq. per litre. These findings seemed to support a diagnosis of either Addison's disease or salt-losing nephritis.

When admitted to hospital in July, 1956, for investigation, he was unexpectedly found to be pyrexial, his temperature running a continuous irregular course up to 102·8°F. A few days later he had some small (1–1·5 cm. diameter) non-tender raised erythematous subcutaneous nodules on the left calf, and later one appeared on the left forearm; each nodule lasted about four days. He said these were the " lumps " he had complained of since 1954. His blood-pressure, which was 120/75 on admission, fell at times to 90/65. Investigations were therefore made to determine (*a*) whether he had Addison's disease, and (*b*) the cause of his persistent pyrexia.

Investigations

Examination of his blood showed: Hb 60% (8·9 g. per 100 ml.), red-cell count 3·3 million per c. mm., leucocytes 12,400 per c. mm. (polymorphs 68%), and E.S.R. 55 mm. in one hour. His serum-electrolyte levels were: sodium 126, potassium 6·4, and chloride 90 mEq. per litre. The blood-urea was 37 mg. per 100 ml. In the sputum no tubercle bacilli were seen or cultured, but *Hæmophilus influenzæ* was cultured, and found to be sensitive to penicillin. The urine contained protein 5 mg. per 100 ml., no cells, and no casts; culture was sterile, and no acid-fast bacilli were seen or cultured. No pathogens were isolated from the stools. Serum-agglutinations were negative. Three blood cultures were sterile. The Wassermann and Kahn reactions were negative. Chest radiographs were normal. Plain X-rays of the abdomen revealed no suprarenal calcification, and an intravenous pyelogram showed good excretion on both sides, and normal anatomy. The Mantoux test at 1/10,000 gave an intensely positive reaction, with 1·5 cm. of induration and 3 cm. of erythema, which lasted for over ten days. The absolute eosinophil-count was only 23 per c. mm., and the twenty-four-hour excretion of 17-ketosteroids was 6·4 mg. After a slow intravenous infusion of corticotrophin 30 mg. the eosinophil-count was 27 per c. mm. and the 17-ketosteroid excretion was 6·8 mg., but the low eosinophil-counts invalidated this part of the test (Nabarro 1958). His urinary output after drinking 1000 ml. of water was only 530 ml. (normal 900–1000 ml.) in four hours (Nabarro 1958, Soffer and Gabrilove 1952).

From these investigations we concluded that this was a case of Addison's disease, and that the fever was the result of active tuberculous suprarenal infection. Penicillin 500,000 units six-hourly for ten days had no effect on the fever.

Treatment and Progress

The patient was initially treated by mouth with sodium chloride 3 g. per day, later increased to 6 g. per day, together with copious fluids. This kept his blood-pressure at about 100/70.

In August we decided to treat him with intramuscular streptomycin, 1 g. twice daily for five days then 1 g. daily, isoniazid by mouth, 100 mg. twice daily, and intramuscular deoxycortone 5 mg. daily. This had a most dramatic effect on his illness, and within five days his pyrexia had completely settled although he had been continuously febrile for the previous month. He gradually gained strength and appetite, his weight increased by 14 lb., and his blood-pressure gradually rose, reaching 150/85 by the end of five weeks' treatment. The plasma-sodium was 135 and the plasma-potassium 5·1 mEq. per litre.

Towards the end of October the daily injections of deoxycortone were replaced by a single intramuscular depot injection of 125 mg. of deoxycortone trimethyl acetate (5 ml. of ' Percorten M '). This was repeated a month later, and was then stopped because the blood-pressure had gradually risen. By the beginning of January, 1957, his blood-pressure was 180/120, and his serum-sodium was 141 mEq. per litre. His daily salt supplement was stopped at this time. A fortnight later the blood-pressure had fallen to 160/90, and he continued to feel very well.

At this stage, the slow intravenous infusion of corticotrophin 30 mg. caused the eosinophil-count to fall from 210 to 81 per c. mm., but the urinary 17-ketosteroid excretion did not increase. This result, together with the normal blood-pressure and electrolyte levels, suggested that suprarenal function was returning to normal. The streptomycin injections were stopped in November, 1957, and replaced by *p*-aminosalicylic acid (P.A.S.) 15 g. daily, while the isoniazid was continued.

When the patient was discharged from hospital at the end of January, 1957, his weight was 9 st. 10 lb. (normal for him),

Hb 91% (13·2 g. per 100 ml.), E.S.R. 8 mm. in one hour, and blood-pressure 155/100. He was having no treatment for his Addison's disease. The isoniazid was continued until April, when it was replaced by streptomycin 1 g. three times a week with P.A.S.

In May he returned to full work, feeling perfectly fit and having no complaints. He weighed 9 st. 11 lb., and his blood-pressure was 135/80. Chemotherapy was stopped in June, 1957. He is still quite fit, and his skin pigmentation has disappeared. His serum-electrolytes are normal, and his weight is steady. There is still no evidence of suprarenal calcification.

Discussion

This patient presented with clinical and biochemical features of Addison's disease, including striking malaise and loss of weight, and with pyrexia. Investigations revealed no cause for the fever apart from tuberculosis, and penicillin in full doses had no effect on it. We therefore concluded that the fever was caused by active tuberculosis of the suprarenals, and this was supported by the fact that chemotherapy with streptomycin and isoniazid rapidly brought about improvement. After several months' treatment there was a complete remission of signs and symptoms. The skin lesions, which were presumably tuberculides, have not recurred since treatment began.

The reason we did not use cortisone in this case was because just previously another case of Addison's disease with active pulmonary tuberculosis, treated with cortisone, had rapidly developed tuberculous bronchopneumonia and died eight weeks later, despite apparently adequate chemotherapy.

In the earlier stages of our investigations salt-losing nephritis was considered as a possible alternative diagnosis but there was no evidence of nephritis except occasional albuminuria.

Before chemotherapy was given, salt and deoxycortone proved essential to maintain the patient's blood-pressure and plasma-sodium level, but later both became unnecessary, and indeed he developed hypertension necessitating their withdrawal. At present he is fit and apparently " cured ". Further plain radiographs of the suprarenal area have unfortunately shown no evidence of suprarenal calcification which would clinch the diagnosis. Our experience suggests that more reliance might be placed on chemotherapy in some cases of tuberculous Addison's disease.

Summary

An unusual case of Addison's disease, presenting with fever, was apparently " cured " with antituberculous drugs.

REFERENCES

Nabarro, J. N. D. (1958) Biochemical Investigations; p. 233. London.
Soffer, L. J., Gabrilove, J. L. (1952) *Metabolism*, **1**, 504.
Simpson, S. L. (1956) *in* Price's Textbook of the Practice of Medicine; p. 510. London.
— (1959) Major Endocrine Disorders; p. 161. London.
Spence, A. W. (1953) Clinical Endocrinology; p. 277. London.

" . . . in pulmonary tuberculosis we have seen steadily declining death-rates which effective chemotherapy has greatly accelerated in the past decade. This has led to undue optimism and to pronouncements that tuberculosis is ' on the run,' is a disappearing disease. The facts are very different. Tuberculosis is today probably the most important infectious disease in the world, taking precedence over malaria in its ravages and economic effects."—Prof. ROBERT CRUICKSHANK, F.R.C.P., *Measurements in Medicine*; p.35. Edinburgh: Royal College of Physicians. 1961.

HÆMOPHILIA A IN A GIRL

A Probable Exception from Sex-linked Recessive Inheritance

A. DE LA CHAPELLE
M.D. Helsinki
OF THE MINERVA FOUNDATION INSTITUTE FOR MEDICAL RESEARCH, HELSINKI, FINLAND

E. IKKALA
M.D. Helsinki

H. R. NEVANLINNA
M.D. Helsinki
OF THE FINNISH RED CROSS BLOOD-TRANSFUSION SERVICE, HELSINKI

A FEMALE hæmophiliac must be homozygous for the gene causing hæmophilia, and this gene combination was regarded as lethal by Bauer (1922). In 1950, however, Brinkhous and Graham found that it was possible to produce homozygous female dogs with hæmophilia. Marriages have since been reported between an affected male and a carrier, the female children being homozygous hæmophiliacs (Israëls et al. 1951, Merskey 1951, Pinniger and Franks 1951, Pola and Svojitka 1957, Wilkinson et al. 1957, Stefanovic et al. 1959).

Quick and Hussey (1958) and Choremis et al. (1956) have reported female cases of hæmophilia with a negative family history.

Nilsson et al. (1959) reported a girl with severe hæmophilia A. The patient was a daughter of a carrier,

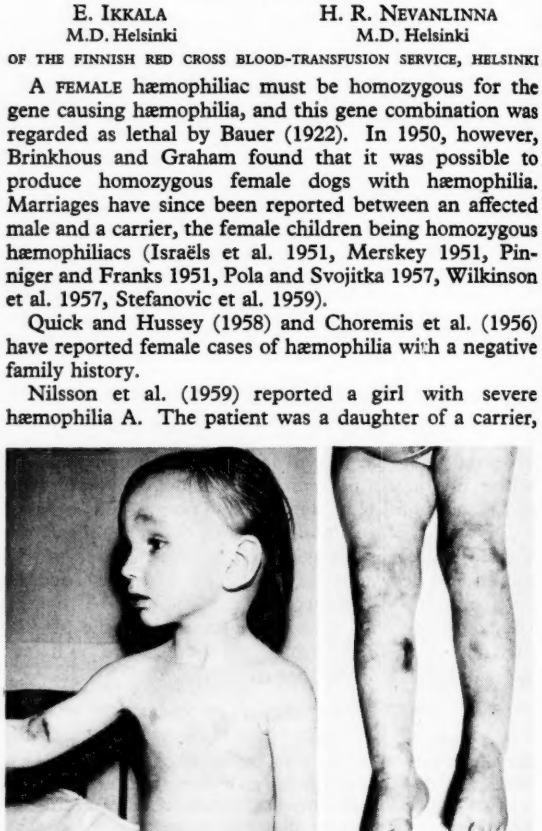


Fig. 1—The patient in 1958.

but her father was healthy. Chromosomal studies, however, explained this apparent exception from sex-linked inheritance. The patient was shown to have an XY sex-chromosomal constitution, and a male sex-chromatin pattern.

The present report deals with a girl with severe hæmophilia—a case previously reported by Ikkala (1960). The patient, a daughter of a carrier and a healthy father, has been re-examined and detailed chromosome studies have been made.

Case-report

The patient was born in 1956. At 1 year she was found to sustain large bruises very readily, especially in the gluteal region. Later she had several episodes of protracted epistaxis, hæmarthroses in the knees and ankles, and hæmaturia. Clinical examination revealed nothing to suggest that she was not a normal female (fig. 1).

Family History

The patient belonged to a large family with hæmophiliacs in six generations. The oldest generations were reported by Nordberg (1895). Except for the present patient there have been

no exceptions from the normal transmission of the hæmophilic gene (fig. 2).

The patient's father had a history of perfect health, and coagulation studies gave normal results. A blood-group study (ABO, MN, and Rh subgroups C, D, E, c) gave no reason to suspect his paternity.

The patient's mother had no bleeding symptoms, but in coagulation studies she had a slightly increased antihæmophilic globulin (A.H.G.) percentage—50–60% or normal.

The patient's elder brother had had perfect health. The other brother (VII, 10), who was born in 1952, and two more remote relatives (VI, 12 and VII, 5) had typical severe hæmophilia A, both clinically and in laboratory examinations. The other hæmophiliacs of the family were already dead, their diagnoses resting on anamnestic data.

Coagulation Studies

These were performed by the methods of Ikkala (1960), and the patient was examined on three different occasions. The

TABLE I—THE PATIENT'S RECALCIFICATION-TIME, PROTHROMBIN-CONSUMPTION INDEX, AND A.H.G. PERCENTAGE, ON THREE DIFFERENT OCCASIONS

Date	Recalcification-time (secs.)	Prothrombin-consumption index	A.H.G. assay	
			T.G.T. method (%)	Recalcification method (%)
February, 1958	740	104	1, 5	
October, 1958	610	120	2	1, 5
December, 1960	730	100	1	2
Normal range	90–240	32–70	60–140	50–200

TABLE II—CHROMOSOME-COUNTS FROM 100 CELLS

—	Chromosome-counts				Total
No. of chromosomes ..	<45	45	46	47	>47
No. of cells	1	1	95	3	100

Platelet-count was 280,000–400,000 per c.mm., the bleeding-time always being less than 4 minutes. The prothrombin-time (Quick), prothrombin, factor V, factor VII, and factor IX determinations gave normal results. No circulating anticoagulants were found (table I). The laboratory findings are thus typical of severe hæmophilia A.

Cytological Studies

The sex-chromatin pattern of the patient was female. Of

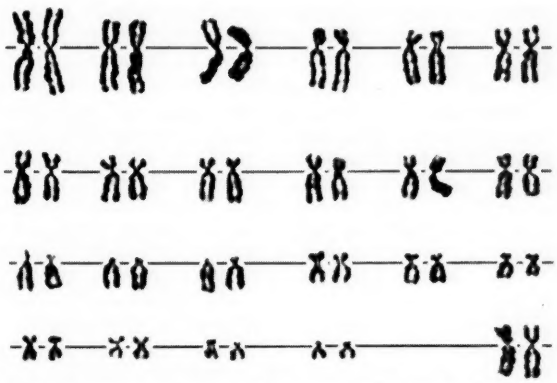


Fig. 3—Chromosomes arranged in pairs: normal female karyotype.

five hundred polymorphonuclear leucocytes from peripheral blood twenty-three had typical drumsticks. In smears from oral mucosa, sex-chromatin bodies were present in about 50% of the cells. No leucocytes with two drumsticks, and no cells with two or more sex-chromatin bodies, were found.

The chromosomes were studied by the method of Hungerford et al. (1959), as modified slightly by Jacobs (1960). Leucocytes were separated from erythrocytes, incubated with growth medium, and treated with demecolcine (' Colcemid ', Ciba) and hypotonic citrate. Air-dried preparations were stained with orcein. No squashing was done. A hundred suitable cells with the chromosomes in metaphase were selected, and the chromosomes of these cells were counted under a light microscope (table II).

Leucocyte cultures were set up on two different occasions, and cells from both experiments were used for counting the chromosomes. No difference was noticed between cells from the two experiments. Five cells with a chromosome number different from 46 were all analysed. The aberrant number seemed to be the result of broken chromosomes. In three cells with 47 chromosomes the additional elements turned out to be fragments of various broken chromosomes.

Of the cells with 46 chromosomes twenty were analysed both by drawing and photographing. All these had a chromosome complement typical of a normal female, including 2 chromo-

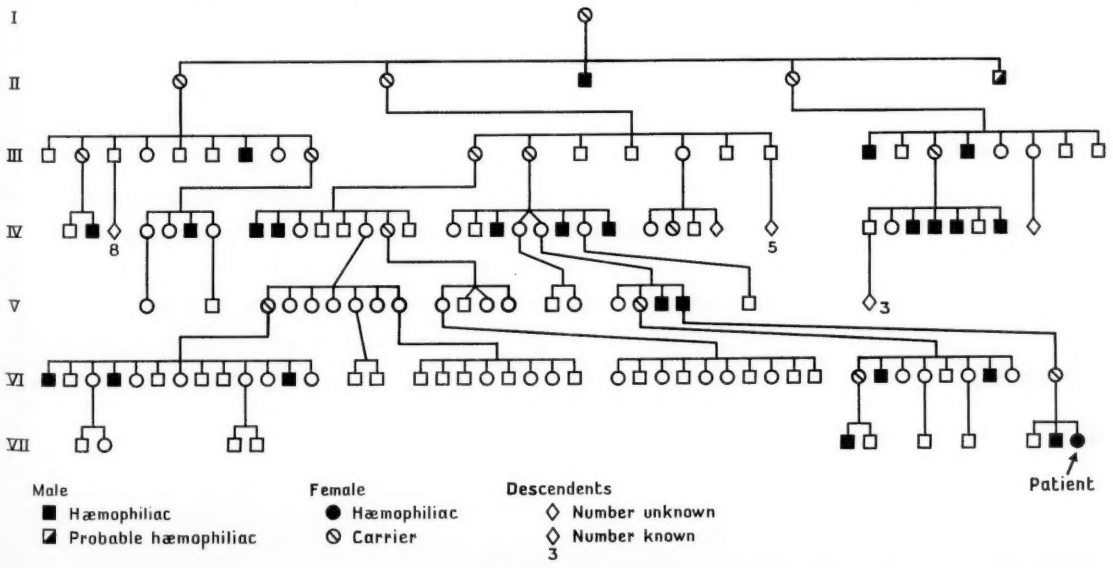


Fig. 2—Pedigree of the family.

somes which were thought to be normal X-chromosomes. The chromosome idiogram of the patient, arranged according to the Denver classification (1960), is shown in fig. 3.

Discussion

The patient was examined three times, and each gave results typical of severe hæmophilia A. Female carriers of hæmophilia are known to have slightly decreased levels of A.H.G., and occasionally mild bleeding symptoms. The patient's coagulation defect and the severity of the symptoms suggest that this possibility can be excluded in the case here reported. She was, we believe, a real hæmophiliac.

The case of Nilsson et al (1959) was similar to ours: the patient was a daughter of a carrier and a healthy father. In their case chromosome studies clarified the apparent exception from sex-linked inheritance by revealing the presence of male sex-chromatin and male chromosomes. Our patient differed from that of Nilsson et al. in being a female not only clinically but also according to the cytological investigations of both sex chromatin and chromosomes. The chromosome complement could not be distinguished from that of a normal female, and there was no evidence of chromosomal mosaicism. Mosaicism would be more easily demonstrable in cultured cells from other tissues—e.g., skin and bone-marrow—but the presence of a normal number of sex-chromatin bodies in cells of the oral mucosa weighs against this view. Theoretically any mosaicism having cells with an XO or XY constitution would explain the hæmophilia in a " female " with a normal father. There is, however, no reason to believe that the chromosome complement in our case was not that of a normal female.

The hæmophilia cannot be simply explained in this case. One possibility is that the girl's real father was a hæmophiliac. In the blood-group studies nothing was found to make the paternity suspect. In addition one must remember that the number of hæmophiliacs in the fertile period of life is small and that their capacity for extramarital relations is almost certainly decreased.

Another possible explanation is that there was a non-disjunction in the second meiotic division both in the spermatogenesis of the father *and* in the oogenesis of the mother. Thus an ovum with 24 chromosomes and 2 X-chromosomes, both carrying the gene for hæmophilia, may have become fertilised by a sperm-cell containing 22 chromosomes but no sex chromosomes. As the incidence of non-disjunction in man is unknown, we cannot calculate the likelihood of a simultaneous occurrence of this phenomenon in both father and mother.

A third possibility is that mutation towards hæmophilia occurred in the X-chromosome inherited from the father. Assuming that the mutation-rate is 3.2×10^{-5} per X-chromosome and generation (Ikkala 1960), the mutation-rate in the father's X-chromosome would be one third of this—i.e., 1 in 94,000. The number of hæmophiliacs born is about 1 in 6500 (Ikkala 1960). The number of carriers depends on the fertility of the hæmophiliac patients; the ratio between carriers and patients is more than 1/1 and probably less than 2/1. Thus the possibility of a child inheriting from the mother a hæmophilic X-chromosome, and of a mutation towards hæmophilia occurring simultaneously in the X-chromosome inherited from the father, would be one in several hundred million births.

Summary

Severe hæmophilia A in the daughter of a carrier and a healthy father is reported. The patient was a female both clinically and in the light of chromosome studies.

The possible explanations for the exception from normal sex-linked recessive inheritance are discussed.

REFERENCES

Bauer, K. H. (1922) *Dtsch. Z. Chir.* **176**, 109.
Brinkhous, K. M., Graham, J. B. (1950) *Science*, **111**, 723.
Choremis, K. B., Zervos, N., Tsevrenis, H., Apostopoulou, E., Mandalaki, T. (1956) *Helv. paediat. acta*, **3**, 305.
Denver Classification (1960) *Lancet*, i, 1063.
Hungerford, D. A., Donnelly, A. J., Nowell, P. C., Beck, S. (1959) *Amer. J. hum. Genet.* **11**, 215.
Ikkala, E. (1960) *Scand. J. clin. Lab. Invest.* suppl. 46.
Israëls, M. C. G., Lempert, H., Gilbertson, E. (1951) *Lancet*, i, 1375.
Jacobs, P. A. (1960) Personal communication.
Merskey, C. (1951) *Quart. J. Med.* **20**, 299.
Nilsson, I. M., Bergman, S., Reitalu, J., Waldenström, J. (1959) *Lancet*, ii, 264.
Nordberg, A. (1895) *Finska Läksällsk. Handl.* **37**, 94.
Pinniger, J. L., Franks, R. B. (1951) *Lancet*, ii, 82.
Pola, V., Švojitka, J. (1957) *Folia Haemat., Lpz.* **75**, 43.
Quick, A. J., Hussey, C. V. (1958) *Lancet*, i, 1294.
Stefanovic, S., Rolovic, Z., Zujevic, J. (1959) *Sang.* **30**, 858.
Wilkinson, J. F., Israëls, M. C. G., Nour-Eldin, F., Turner, R. L. (1957) *Brit. med. J.* ii, 1528.

PENNYROYAL: A RARE CAUSE OF EPILEPSY

DONAL F. EARLY
L.R.C.P.I., D.P.H., D.P.M.
CONSULTANT PSYCHIATRIST,
SOUTHMEAD HOSPITAL AND MANOR PARK HOSPITAL, BRISTOL

REFERENCES to side-effects of pennyroyal in standard textbooks are uncommon and mostly cursory, though this drug is freely available without prescription, and may be taken as an abortifacient.

Smith and Fiddes (1955), Martindale (1958), and Brend (1941) all briefly mention nervous involvement and convulsions.

The following case of epilepsy caused by pennyroyal is the first published in which electroencephalographic recordings have been made.

Case-report

A woman of 23, who had had two children, was admitted as an emergency to Southmead Hospital, Bristol, on Feb. 4, 1958. Her husband woke the previous night to find her shaking uncontrollably. He could not rouse her. However, she got up normally in the morning, and prepared his breakfast as usual. At 10 A.M. she had another fit, and was found alone in the house by a neighbour, in a dazed state. She had cut her head, and vomited. She had three more fits before midday, one of which was witnessed by her own doctor. He found no physical abnormality except that her temperature was 99°F and pulse-rate 130; and he gave her phenobarbitone injection 200 mg. intramuscularly. She had a further fit at 1 P.M. and at 2 P.M. was again seen by her doctor. At that time she was restless and periodically drowsy. Seen again at 3.45 P.M. she was conscious and rational. her temperature was 100°F and pulse-rate 95. Her blood-pressure was 120/60 mm. Hg; and there were no meningeal signs. At 4.30 P.M. a further fit was witnessed by her doctor who injected paraldehyde 3 ml. intramuscularly, and arranged her admission to hospital.

There was no history of epilepsy, convulsions, fainting attacks, or dizzy spells. She had two children, aged six and four years. Except for epistaxis of unknown origin, she had seen a doctor only when she was pregnant. In an earlier pregnancy pre-eclamptic toxæmia with persistent albuminuria had developed at thirty-four weeks. She had recently missed a menstrual period.

At Southmead Hospital no abnormality of the cardiovascular, abdominal, or respiratory systems was found. Her blood-pressure was 135/90. Soon after admission she had two major epileptic convulsions. Between the fits she was drowsy. After one of them both plantar reflexes were extensor; but no other signs of central nervous involvement were elicited.

Her fits were controlled by phenobarbitone and paraldehyde. On her second day in hospital she was periodically confused but rousable. When lucid, she said she had taken some " red medicine " and a short course of pennyroyal. On the third

day she became violent, grossly confused, and uncooperative. She was transferred to the psychiatric observation ward of Manor Park Hospital.

On admission to this ward she was resistive. She said that she could see relatives and strange men in the ward, a car waiting to take her home, and her husband beating her six-year-old daughter until the child was "red and raw". She was also aurally hallucinated, claiming that she heard a voice telling her "You must go home". She was completely disorientated in time and in space. She had, however, no physical abnormality.

She was treated conservatively, and had no further fits. Two days after admission to the ward and five days after the onset of her illness, she was clear mentally. She said that she had been taking three tablets of pennyroyal 3–4 times daily for about four days before her convulsions started.

Next day, an electrocephalogram was abnormal with epileptic characteristics:

Delta: Moderate amplitude waves from both frontal lobes, but more prominent in the left hemisphere where they spread back into the temporal lobe.

Theta: Moderate potential at 4–6 cycles per second from all areas.

Alpha: Moderate amplitude at 9–10 cycles per second arising posteriorly and responsive to physical stimuli.

Beta: Low-amplitude activity from all areas.

Sharp waves and spikes: Frequent random moderate-amplitude activity from all areas, but most marked in the frontal lobes and in the left hemisphere, often forming complex paroxysms which spread into the temporal lobes.

Evoked responses: Hyperpnœa: Augmented the slow activity. Photic stimulation: Added no further information.

She remained settled and twenty-four hours later was discharged to the care of her own doctor.

Electroencephalography was repeated one month later. It was normal.

Alpha: Moderate amplitude at 8–9 cycles per second arising posteriorly, spreading forward persistently, and responsive to physical stimuli.

Evoked responses: Hyperpmœa and photic stimulation: Added no further information.

Her Friedman test was positive. She had no further fits, and has remained clinically well until now. She was delivered of a normal girl on Aug. 23, 1958.

Discussion

Wingate (1889) described unconsciousness and convulsions in a woman of 20, who was four months pregnant. He witnessed two convulsions during which "the body gradually and methodically assumed the position of extreme opisthotonos . . .". After vomiting, the patient regained consciousness. She had taken a teaspoonful of oil of pennyroyal and half a teaspoonful of fluid extract of ergot about two hours previously. "She talked incoherently for a few hours afterward."

Kimball (1898) observed one "general convulsion, tonic in character" after ingestion of "at least one ounce" of oil of pennyroyal by a pregnant woman of 23.

Holland (1902) reported the case of a woman of 24 with a history of one week's amenorrhœa who took half a drachm of oil of pennyroyal and, within an hour, "had lost consciousness and was seized with a violent tonic contraction of all muscles, opisthotonos being well marked. This spasm lasted only a few minutes and left the patient talking incoherently and tossing about the bed". This "attack" was not witnessed by Holland who found the patient conscious when he arrived.

Other reports of pennyroyal poisoning (Wilcox 1869, *Southern Clinic* 1883, Girling 1887, Flynn 1893, Stephen 1894, Allen 1897, Runnals 1904, Braithwaite 1906, Vallance 1955) do not mention fits.

Our patient, six weeks pregnant, and with no previous or subsequent evidence of epilepsy, had an acute epileptic attack, followed by a severe psychotic confusional episode after ingesting pennyroyal and a "red" medicine. The latter proved to be 'Widow Welch's female pills', a mixture of ferrous sulphate, sulphur, liquorice, and turmeric. It is, therefore, clear that her convulsions were related to pennyroyal.

As this drug is freely available it is surprising that such cases have not been reported more often. I have found in the literature only three cases in which convulsions have been described. This possibility should be kept in mind when investigating epilepsy arising de novo in pregnant women.

The electroencephalographic findings are interesting. The abnormal characteristics were most marked anteriorly and showed a left-sided preponderance. After four weeks the electroencephalogram was normal.

Summary

Epilepsy developed in a woman of 23, who took pennyroyal to procure abortion.

The electroencephalogram gave evidence of cerebral dysrhythmia. This cleared completely in four weeks.

I should like to thank Dr. G. E. F. Sutton, formerly consultant physician, Southmead Hospital, Bristol, who invited me to see this patient; Dr. E. C. Turton, formerly consultant psychiatrist in charge of the department of electroencephalography, Barrow Hospital, Bristol, for the electroencephalograms; and Dr. K. D. Davies, her family practitioner, for help in following her up.

REFERENCES

Allen, W. T. (1897) *Lancet*, i, 1022.
Braithwaite, P. F. (1906) *Brit. med. J.* ii, 865.
Brend, W. A. (1941) Handbook of Medical Jurisprudence and Toxicology; p. 298. London.
Flynn, E. F. (1893) *Brit. med. J.* ii, 1270.
Girling, J. (1887) *ibid.* i, 1214.
Holland, G. W. (1902) *Virginia med. Semi-Mon.* **7**, 319.
Kimball, H. W. (1898) *Atlant. med. Wkly*, **9**, 307.
Martindale's Extra Pharmacopœia (1958) London.
Runnals, H. B. (1904) *Med. Sent.* **12**, 325.
Smith, S., Fiddes, F. S. (1955) Forensic Medicine. London.
Southern Clinic (1883) **6**, 323.
Stephen, W. H. (1894) *Provin. med. J., Leicester*, **13**, 966.
Wilcox, W. A. (1869) *Boston med. surg. J.* **79**, 394.
Wingate, V. O. R. (1889) *ibid.* **120**, 538.
Vallance, W. B. (1955) *Lancet*, ii, 850.

Preliminary Communications

PHOSPHORYLASE ACTIVITY IN LEUCOCYTES FROM PATIENTS WITH GLYCOGEN-STORAGE DISEASE

THE diagnosis of the particular type of glycogen-storage disease can usually be made with certainty only by investigation of the enzymes involved in the glycogen metabolism of the affected tissues. It appears that blood is one of the tissues in which a defect in glycogen metabolism can manifest itself. In 1934 van Creveld [1] showed that the blood of two patients suffering from glycogen-storage disease contained an increased amount of glycogen. According to Wagner [2] the presence of glycogen in the blood of normal individuals is solely due to its presence in leucocytes, since none could be demonstrated in other blood corpuscles or in plasma. In the blood of a patient suffering from glycogen-storage disease, Wagner [3] found glycogen in the plasma as well as considerably increased amounts in the leucocytes. However, Sidbury et al.[4] have recently demonstrated the presence of small amounts of glycogen in normal erythrocytes. They found, moreover, that an ætiological diagnosis of types III and IV

1. van Creveld, S. *Arch. Dis. Childh*, 1934, **9**, 9.
2. Wagner, R. *Arch. Biochem.* 1946, **11**, 249.
3. Wagner, R. *Amer. J. Dis. Childh.* 1947, **73**, 559.
4. Sidbury, J. B., Jr., Cornblath, M., Fisher, J. *Pediatrics*, 1961, **27**, 103.

PHOSPHORYLASE ACTIVITIES OF LEUCOCYTE EXTRACTS

Sex and age (years) of patient	History of glycogen-storage disease	Enzyme deficiency in liver biopsy material	Phosphorylase activity in leucocyte extracts (mμmoles glucose 1-phosphate formed per mg. protein per hour)
B Female (6)	−		179
H Male (2)	−		108
W Male (2)	−		75
L Female (2)	−		79
R Female (3)	−		133
M Female (adult)	−		83
C Male (2)	+	Phosphorylase	17
Mother of C	−		17
Father of C	−		83
K* Male (3)	+	Phosphorylase	17
Ke* Male (7)	+	Phosphorylase	17
Wa† Female (18)	+	Glucose 6-phos-phatase	94
G* Male (9)	+	Glucose 6-phos-phatase	68
Br Male (9)	+		19
Mother of Br	−		44
Sister of Br (11)	−		23

* Patient of Dr. Tegelaers.
† Patient of Dr. Fernandes.

of glycogen-storage disease could be made by assay of the concentration and chemical structure of the erythrocyte glycogen.

An accumulation of glycogen in leucocytes from patients with glycogen-storage disease could be due to phagocytosis of glycogen derived from other affected tissues or to a disturbed glycogen metabolism in the leucocytes themselves. Consideration of the second possibility led us to the present investigation, since diagnosis will be facilitated if a disturbed enzymic pattern in leucocytes reflects an enzymic defect in other related but less easily obtainable cells.

MATERIALS AND METHODS

5 ml. of blood was collected in heparin and immediately placed in ice. All subsequent procedures were carried out in the cold (0–5°). The blood was centrifuged for 5 min. in a clinical centrifuge at 3000 r.p.m. and the plasma was removed by suction. By rotating the residue the film of leucocytes could be attached to the wall of the centrifuge tube, so that the majority of red cells could be removed by suction. The film of leucocytes was then washed 5–10 times with cold 0·15 *M* KCl and finally twice with cold water (water twice-distilled in glass was used throughout) in order to lyse most of the adhering red cells and thrombocytes. The packed leucocytes were then transferred to a small Potter-Elvehjem homogenizer with the help of 2 ml. cold 0·01 *M* sodium phosphate buffer, pH 7·5. The leucocytes were then homogenized in the cold in this small amount of phosphate buffer using a hand-operated Teflon pestle. The resulting homogenate was then centrifuged in small plastic tubes in a Servall angle-head centrifuge for 15 min. at 19,000 *g*. The clear pink supernatant was used in the spectrophotometric assay of phosphorylase activity.

Spectrophotometric Determination of Phosphorylase Activity

The method used was that of Wu and Racker as described by Schmid et al.[5] in which the rate of reduction of triphosphopyridine nucleotide (TPN$^+$) is measured with a limiting concentration of phosphorylase (here the leucocyte extract) in the presence of excess glycogen, inorganic phosphate, phosphoglucomutase, glucose 6-phosphate dehydrogenase, and TPN$^+$. The excess of the latter two enzymes was always checked by replacing the glycogen and the leucocyte extract by glucose 1-phosphate. The cuvettes (1 cm. light path) contained 50 m*M* tris(hydroxymethyl)aminomethane-HCl buffer (pH 7·5), 12·5 m*M* NaCl, 10 m*M* sodium phosphate buffer (pH 7·5), 2 mg. glycogen (pure oyster glycogen, British Drug Houses) per ml., 0·25 ml. leucocyte extract, phosphoglucomutase (prepared by the method of Najjar [6]), glucose 6-phosphate dehydrogenase (Boehringer), 10 m*M* $MgCl_2$*, and 0·23 m*M* TPN$^+$ in a final volume of 2 ml. The reference cell contained all additions except the TPN$^+$. The reaction was started by the addition of TPN$^+$. The reaction was followed at 340 mμ. for 90 min. at 20° and readings taken every 10 min. No reaction was observed if glycogen was omitted from the incubation medium. The protein content of the leucocyte extract was determined by the method of Warburg and Christian [7] and was corrected for small amounts of hæmoglobin by measuring the absorbancy at 540 mμ and using an absorption coefficient of hæmoglobin of 940 sq. cm. per g. Phosphorylase activities in leucocyte extracts were calculated as mμmoles of glucose 1-phosphate formed per mg. protein per hour, using a molecular extinction coefficient of TPNH of $6{\cdot}22 \times 10^6$ sq. cm. $\times$ mole^{-1} (ref. 8). A hæmolysate of normal erythrocytes in a final concentration equal to that contaminating the leucocyte extracts contained no measurable phosphorylase activity in the test system described (F. Huijing: unpublished observations).

RESULTS AND DISCUSSION

The first six patients not suffering from glycogen-storage disease shown in the table had leucocyte-phosphorylase activities between 75 and 179 mμmoles per mg. protein per hour. A possible explanation for the large variation in activity is a difference in the secretion of epinephrine or glucagon, hormones which have been shown to influence phosphorylase activity. Factors such as emotional excitement, injury, and certain drugs can stimulate epinephrine secretion and therefore are likely to influence the levels of phosphorylase activity.

In three cases of glycogen-storage disease associated with liver-phosphorylase deficiency, first described by Hers,[9 10] the leucocyte-phosphorylase activities were about one fourth of the lowest normal value. The table shows that the mother of patient C also had a low leucocyte-phosphorylase activity. She has no history of glycogenosis in childhood. Two cases of glycogen-storage disease, caused by a deficiency of glucose 6-phosphatase, had leucocyte-phosphorylase values within the normal range.

In one patient with symptoms of liver glycogen-storage disease (Br), a low phosphorylase activity was found in the leucocytes, but no enzymic determination was carried out on liver biopsy material. The mother and sister of Br also had low leucocyte-phosphorylase activities, although they had no history of glycogen storage disease (cf. similar results by Hers [10] relating to the liver-phosphorylase activities).

A preliminary experiment carried out with an aged crude leucocyte homogenate from a normal control indicated that the type of phosphorylase present in leucocytes is more related to liver phosphorylase than to the muscle enzyme, since adenosine triphosphate, in contrast to adenosine monophosphate, was able to reactivate the phosphorylase activity of the crude homogenate (cf. refs. 11 and 12).

These preliminary results suggest that the determination of leucocyte-phosphorylase activity might be of assistance in diagnosing glycogen-storage disease, caused by a deficiency of liver phosphorylase, thereby obviating the necessity for a biopsy. Such determinations might also be useful in detecting carriers of the disorder, who do not show the clinical symptoms.

5. Schmid, R., Robbins, P. W., Traut, R. R. *Proc. nat. Acad. Sci., Wash.* 1959, **45**, 1236.
6. Najjar, V. A. *in* Methods in Enzymology (edited by S. P. Colowick and N. O. Kaplan) vol. I, p. 294. New York, 1955.

* This addition was always made just before the TPN$^+$ to the stirred solution, in order to prevent formation of a precipitate of magnesium phosphate.
7. Warburg, O., Christian, W. *Biochem. Z.* 1941, **310**, 384.
8. Horecker, B. L., Kornberg, A. *J. biol. Chem.* 1948, **175**, 385.
9. Hers, H. G. *Rev. int. Hépatol.* 1959, **9**, 35.
10. Hers, H. G. *Chem. Weekbl.* (in the press).
11. Rall, T. W., Sutherland, E. W., Wosilait, W. D. *J. biol. Chem.* 1956, **218**, 483.
12. Wosilait, W. O., Sutherland, E. W. *ibid.* p. 469.

We are very grateful to Prof. H. G. Hers (University of Louvain) for the enzyme determinations on liver biopsy material referred to in the table. We are further indebted to Prof. E. C. Slater for his stimulating interest and valuable suggestions.

W. C. HÜLSMANN
M.D.
Senior Lecturer in Biochemistry
T. L. OEI
Demonstrator in Biochemistry
Laboratory of Physiological Chemistry, University of Amsterdam, Amsterdam, The Netherlands
S. VAN CREVELD
M.D.
Professor of Pædiatrics
Pediatric Clinic, University of Amsterdam

SENSORY TERMINAL DEGENERATION IN ORTHO-CRESYL PHOSPHATE POISONING

THE paralysis caused by o-cresyl phosphate in man is clinically thought to be motor in type.[1–3] But direct evidence of this is scanty; and, since there is little muscular wasting in the first month, it is likely that factors other than motor-nerve degeneration account for the motor weakness. Among these are spinal-tract changes; but the degree to which these operate in relatively minor cases of poisoning is unknown, because necropsy material is available only from those that are badly affected.[4] Clinical evidence of sensory disturbance was seen in some cases in the recent Moroccan outbreak; thus transitory cutaneous

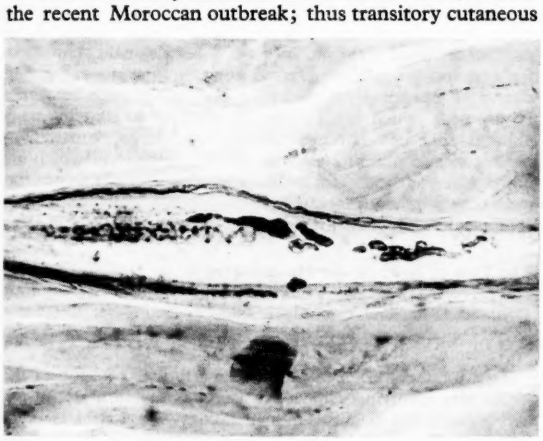


Fig. 1—Muscle spindle in flexor digitorum brevis stained with sudan-black B to show entering myelinated nerve fibre and annulospiral ending. (×165.)

sensory changes were noted [5] in Morocco as in previous outbreaks.[6]

In the present study of the effects of tri-*o*-cresyl phosphate on cats, functional disturbances very closely similar to those met with in man were produced.

Muscular wasting was very slight, but ataxia (sometimes with transient high stepping gait) and motor weakness (with foot drop) were regularly found. The hind limbs were always more affected than the forelimbs. There was the characteristic delay of about two weeks after one or two subcutaneous injections of 0·25–0·5 ml. per kg., and thereafter degeneration of nerve fibres coincided with the onset of symptoms just as it does in the hen.[7] As in poisoned humans and chickens, fibres of fasciculus gracilis and corticospinal tracts in regions most distal from their parent neurones were constantly damaged, but the numbers of degenerating fibres in each tract was relatively small.

1. Wilson, S. A. K. *Neurology*. London, 1954.
2. Hunter, D. The Diseases of Occupations. London, 1955.
3. Smith, H. I., Spalding, M. J. K. *Lancet*, 1959, ii, 1019.
4. Aring, C. D. *Brain*, 1942, **65**, 34.
5. Geoffroy, H., Slomic, A., Benebadji, M., Pascal, P. *Wld Neurol.* 1960, **1**, 294.
6. Burley, B. T. *J. Amer. med. Ass.* 1932, **98**, 298.
7. Cavanagh, J. B. *J. Neurol. Neurosurg. Psychiat.* 1954, **17**, 163.

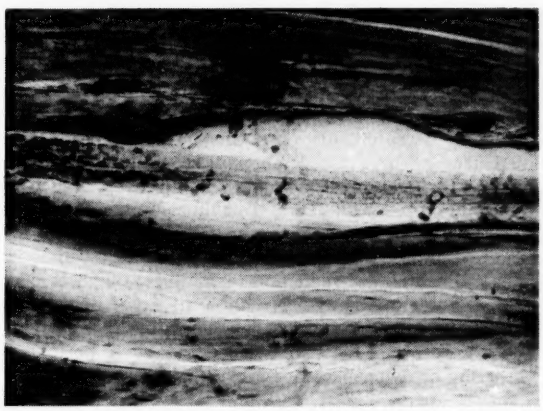


Fig. 2—Muscle spindle as in fig. 1 but from cat 4 weeks after onset of paralysis due to T.O.C.P. (×165.)

The feature of the changes in the peripheral nerves to which we wish to draw attention is the considerable destruction of the sensory terminals of muscle spindles and tendon organs, and the relatively minor changes apparent in motor endings.

These observations are based upon examination of muscles of the foot and leg by intravital methylene-blue, by silver impregnation of axons, by staining of myelin and nerve terminals with sudan-black B, and by the cholinesterase methods. The sudan technique is particularly well suited for this purpose, since it reveals with little technical difficulty degenerating nerve fibres, and clearly shows the annulospiral sensory endings of normal muscle spindles (fig. 1), the club endings of Golgi tendon organs, and the terminal fibre in the core of pacinian corpuscles. It also shows the myelinated motor fibres running to end-plates. Sampling interosseus and flexor digitorum brevis of the foot 20–30 days after injection showed total loss of annulospiral endings (fig. 2) in all muscle spindles, loss of more than half of nerve fibres running to Golgi tendon organs, and destruction of fibres entering pacinian corpuscles. By contrast, the intramuscular bundles of nerve fibres running to motor terminals showed degenerative changes in less than 5% of fibres. There were, however, many motor endings with minor but significant degenerative changes that were shown only with the methylene-blue technique. In tibialis anterior both damaged and normal spindles were found, and normal spindles were also present in gastrocnemius and soleus muscles. The proportion of damaged Golgi tendon organs was also reduced and very few degenerating motor fibres or terminals were found in these muscles.

In the hen [7] distal degeneration of fibres in nerves was found to be greater than proximal degeneration. This

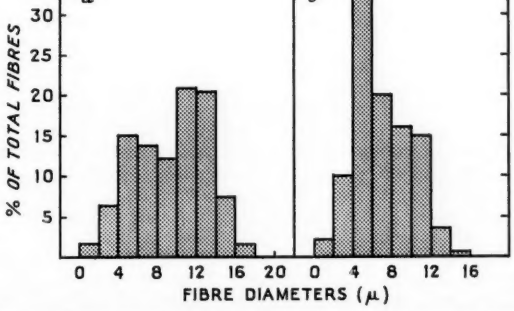


Fig. 3—Histogram showing distribution of fibre diameters in the deep branch of the common peroneal nerve. Left, normal; right, T.O.C.P. 45 days after injection

finding agreed with the distribution of functional changes seen in man and with our present observations on cats. Moreover, since sensory nerves appear to be more affected than motor, it is deduced that fibres of large diameter are selectively damaged, and this is in fact confirmed by fibre diameter measurements. For this purpose the external diameters of myelinated fibres were measured in the manner of Fernand and Young [8] in the deep branch of the common peroneal nerve. In animals in which enough time was given for degeneration (i.e., 30–40 days) the normal bimodal histogram was converted to a unimodal one, through severe reduction in numbers of fibres over 10μ in diameter (fig. 3). No abnormality of dorsal-root ganglion or anterior-horn cells was visible at this time, and the process must be considered as a peripheral withering or dying-back of the affected axons.

These results suggest the following points when considering physiotherapy. Since the nerve-cells and Schwann cells are intact, regeneration and remyelination of peripheral nerve-fibres may be expected, and it is the functional performance of the reinnervated sensory nerve-endings upon which good recovery will depend. This must be especially true in mildly affected cases where the motor terminal changes will probably be relatively slight. In more severe cases, on the other hand, the ultimate functional recovery is likely to depend largely upon the amount of spinal-tract damage, which, as was found in the Hamburg outbreak,[9] may not be clinically revealed for several months—by which time, presumably, peripheral nerves have extensively regenerated.

V. MacD. receives a full-time grant from the Medical Research Council.

Department of Pathology, Guy's Hospital Medical School, London, S.E.1

J. B. CAVANAGH
M.B. Lond., M.R.C.P.
Research Fellow in Neuropathology

Department of Neurology, St. Thomas' Hospital, London, S.E.1

VIOLET MACDERMOT
M.R.C.S.
Research Assistant

8. Fernand, V. S. V., Young, J. Z. *Proc. roy. Soc. B.* 1951, **139**, 38.
9. Parnitzke, K. H. *Psychiat. Neurol. med. Psychol. (Lpz.)*, 1952, **4**, 86.

Reviews of Books

The Nomenclature of Disease

8th ed. Drawn up by a Joint Committee appointed by the Royal College of Physicians of London. London: H.M. Stationery Office. 1960. Pp. 398. 22*s*. 6*d*.

IT was said that a former Principal of the first college in the first university in the Kingdom could detect every misprint in Bradshaw within twenty minutes of receiving his monthly copy. Reviewing this invaluable old friend presents a problem of the same magnitude. The best test of its value is to remember the most bizarre postmortem you ever saw: if used intelligently this book will give a lucid and rational name to the cause of death.

There are inevitably a few omissions and errors. In the "etiological classification" (the spelling is regrettable anywhere and damnable in Pall Mall) fifth disease appears but salmonellosis does not. "Dysentery, malarial" merely describes a symptom of malaria. The list of bacterial parasites is arbitrary and founded on an outdated conception of pathogenic and saprophytic organisms. The list of worms, on the other hand, is so complete that it contains many which are almost certainly harmless to man. *Ascaris lumbricoides* is defined as "an important cause of ascariasis in man". Would the committee care to name some other causes? There is a long list of the intermediate hosts of *Dracunculus medinensis* but none for *Schistosoma spp.*

The catalogue of eponyms is useful and interesting. We are glad to see that Witts' anæmia survives, but does no-one ever refer to Koch's disease? There may be a place called Jake in Georgia, U.S.A., but jake poisoning is probably a portmanteau form of jamake (jamaica) whence comes the ginger the alcoholic extract of which causes the trouble. Farmers' lung and caisson disease are omitted from the list of ailments named from occupation. Dhobi is mis-spelt. The Hunterian chancre owes its name to the exact definition made by the great man and not to the fact that he poxed himself. Dutton too is listed among the victims who gave their names to diseases from which they suffered. He may have caught relapsing fever, but he and Todd were certainly the first to show that the African disease is transmitted by *Ornithodoros moubata*.[1]

These comments are not intended to detract one tittle from the reputation of a book which must remain a cornerstone of rational medicine. We are very grateful to the committee for their labours.

Surgery is Destined to the Practice of Medicine

Sir REGINALD WATSON-JONES, B.SC., M.CH.ORTH., F.R.C.S., F.R.A.C.S.(Hon.), F.R.C.S.E.(Hon.), F.A.C.S.(Hon.), orthopædic surgeon-extra to Her Majesty the Queen. Edinburgh: E. & S. Livingstone. 1961. Pp. 81. 21*s*.

WHEN the Hunterian Orator for 1959 declared himself "a surgeon destined to the practice of medicine" he was echoing the sentiments of John Hunter, who held operations to be "a reflection on the Healing Art" and "a tacit acknowledgment of the insufficiency of surgery". Sir Reginald shows how far orthopædics has progressed towards making redundant almost all operative procedures. The case-records of Agnes Hunt, with which his account is illustrated, contain many photographs of extreme deformities, large tuberculous abscesses, and draining sinuses, all due to diseases which are now amenable to medical treatment. The text of this address well repays reading because it describes vividly an era in orthopædic surgery that is happily now over.

The Use of Isotopes in Hæmatology

L. G. LAJTHA, M.D., D.PHIL., member of the external staff, Medical Research Council, radiobiology laboratory, department of radiotherapy, Churchill Hospital, Oxford. Oxford: Blackwell Scientific Publications. 1961. Pp. 83. 21*s*.

THIS monograph gives detailed descriptions of some of the techniques involving radioactive isotopes that are useful for investigation and diagnosis in hæmatology. Dr. Lajtha assumes that his readers know all about the instruments used in isotope laboratories and about the general techniques of isotope work. The subjects he deals with are blood-volume determinations, techniques using labelled erythrocytes, white cells, and platelets, studies of iron metabolism, and studies of vitamin-B_{12} metabolism. There is a final short chapter on autoradiography. The practical indications for each technique are briefly discussed. Selected references are provided with each chapter. None of the methods described will be new to anyone engaged in this work, but the book draws together a lot of helpful information. For those thinking of applying these methods, it is a useful short account of what can be attempted at present.

Cardiac Problems (*Papers read at three symposia.* The Chest and Heart Association. London: Chest and Heart Association. 1961. Pp. 144. 18*s*. 6*d*.).—This volume contains 17 short talks given at symposia arranged by the Chest and Heart Association in 1957, 1959, and 1960. Some are in casual colloquial vein, but others are more serious and show evidence of careful preparation. Many aspects of cardiac disease and the treatment of heart-failure are discussed, usually rather briefly, and the first sentence of the book—"My problem is to deal with the differential diagnosis of cardiac and respiratory disease in about fifteen minutes"—makes one wonder why experts attempt the impossible.

1. Dutton, J. E., Todd, J. L. *Brit. med. J.* 1905, ii, 1259.

THE LANCET

LONDON 9 SEPTEMBER 1961

Malignant Melanoma

THE relentless progress of malignant melanoma, striking all too often in the prime of life, and, from a trivial beginning, advancing to widespread and fatal dissemination, tends to leave us with a feeling of hopeless resignation. But resignation is in no way justified by the facts: a patient with malignant melanoma of the skin that is promptly and adequately treated has a 25% chance of being still free of disease five years later [1]—a figure that compares favourably with those for cancer of the stomach or bronchus and for average survival of patients with malignant tumours of the breast.

Experience suggests that for a favourable outcome nothing is more important than correct primary treatment. This has been the prerogative of the surgeon; but almost twenty years ago MARGARET TOD [2] made a strong claim for radiotherapy in the control of this disease, and latterly LEDERMAN [3] has pointed out that not all malignant melanomas of the skin are radioresistant. He is critical of the surgeon's approach, which he believes is too often an emotional one, and of the extremely radical resection which he commonly undertakes. CADE,[1] with a personal experience of both forms of therapy that must be almost unique, has some confidence in the efficacy of mega-voltage techniques. He recommends radiotherapy as a supplement to surgery at the periphery of the excised area, and for the control of an irremovable primary or of recurrent nodules beyond any reasonable hope of surgical resection. On the whole, experience in the treatment of malignant melanoma by means of chemotherapeutic agents has so far not been encouraging. When the disease is largely confined to a limb it can be treated by the perfusion technique developed by CREECH et al.[4] The local and general complications are, however, considerable.[5] Attempts have been made to safeguard the marrow against aplasia by removing some of it and later replacing this when the perfusion has been completed, but this is an exacting technique [6] whose usefulness has not yet been established.

An essential preliminary to adequate treatment is accurate and prompt diagnosis. It is now widely recognised that not all pigmented tumours are melanomas and that not all pigment is melanin; but needlessly extensive operations are still carried out all too often after a mistaken diagnosis of melanoma. Some of the difficulty in diagnosis stems from understandable reluctance to resort to biopsy lest disturbance of a malignant tumour precipitate a shower of metastases. This reluctance may lead to that disturbing state of affairs where, after a wide and disabling operation, examination of the resected specimen fails to confirm a clinical diagnosis of malignant melanoma. Experience seems to sanction the practice of MCNEER,[7] who would allow biopsy of a small lesion and is willing to wait a few days for a paraffin section as a preliminary to definitive treatment. But many would not condone, as he does, the taking of a small biopsy fragment from the summit of an ulcerating lesion or of a darkly pigmented area from a large lesion measuring 5 cm. or more across.

Although a single incident of irritation, physical or chemical, may apparently precipitate the appearance of metastases from a small malignant melanoma, there is no good evidence to suggest that a simple lesion can ever be converted in this way to a malignant one. There is, in fact, remarkably little factual evidence to support the belief that even injury repeated over a long period has this effect. Yet fear of such an effect often leads to the removal of all pigmented skin lesions which appear to be vulnerable to repeated trauma, be it from comb, razor, corset, garter, or shoe—a policy which, as EWING and POWELL [8] showed, is bound to result in many unnecessary operations. There is, by contrast, mounting evidence of an association between exposure to sunlight and the development of malignant melanoma. The relation between the two is unlikely to be as close as in other forms of skin cancer; but, as in other forms, fair-skinned Nordic people are the most vulnerable. In the North American continent the incidence of malignant melanoma of the skin on the face, head and neck, and arms is significantly higher in the south than in the north or west,[9] even though the incidence in whites is about six times that in non-whites. In the southern hemisphere LANCASTER [10] has found a steady rise in the death-rate from malignant melanoma from the relatively sun-starved orchards of Tasmania in the south to the cloudless skies of Western Queensland in the north. The numbers of deaths from malignant melanoma per 1,000,000 persons per year in 1950–53 were for Tasmania 8, Victoria 8, New South Wales 15, and Queensland 23. For Australia as a whole the figure was 13, which contrasts strikingly with 7 for England and Wales and 5 for Scotland.

Certain features in the behaviour of malignant melanoma have encouraged the belief that it may be, in some degree, hormone-dependent. For example, this tumour is rare in childhood, and the prognosis is commonly thought to be better in women than in men and better before than after the menopause. But such attempts as have been made, by ablation of the ovaries, the adrenals, or the hypophysis, to stay the progress of disseminated malignant melanoma have met with no success. Clinicians have believed hitherto that pregnancy exerts an adverse influence on the natural

1. Cade, S. *Ann. R. Coll. Surg. Engl.* 1961, **28**, 331.
2. Tod, M. C. *Lancet*, 1944, ii, 532.
3. Lederman, M. *Proc. R. Soc. Med.* 1961, **54**, 485.
4. Creech, O., Jr., Ryan, R. F., Krementz, E. T. *J. Amer. med. Ass.* 1959, **169**, 339.
5. Irvine, W. T., Noon, C. F. *Proc. R. Soc. Med.* 1961, **54**, 483.
6. Westbury, G., Humble, J. G., Newton, K. A., Skinner, M. E. G., Pegg, D. E. *Lancet*, 1959, i, 968.
7. McNeer, G. *J. Amer. med. Ass.* 1961, **176**, 1.
8. Ewing, M. R., Powell, T. *Brit. J. Surg.* 1951, **38**, 442.
9. Morbidity from Cancer *in* the U.S. Public Health Monograph, 1958, no. 56.
10. Lancaster, H. O. *Med. J. Aust.* 1956, i, 1082.

history of pigmented skin tumours. It is certainly true that in the later months of pregnancy the distribution and depth of pigmentation of the skin may change strikingly and a benign melanoma may become noticeably darker. But there is no reason to believe that this increase in pigmentation heralds any new development in the natural history of a melanoma. Valuble data on the relation between pregnancy and malignant melanoma have been reported by GEORGE et al.,[11] who studied a group of 115 women in whom malignant melanoma and pregnancy coincided, and a control series in which malignant melanoma was not associated with pregnancy. Although at the time of definitive treatment there were rather more women with metastases in the pregnant group than in the non-pregnant control series, the progress of the tumour thereafter did not differ between the two groups. There was no hint of any increased rate of growth or of dissemination in the pregnant women, and their chance of survival at five years was little different. Likewise, WHITE et al.[12] have found that pregnancy does not affect the chance of survival at five years. If, on this evidence, we can be reasonably certain that pregnancy is not responsible for initiating malignancy in a benign melanoma or inducing metaplasia in a malignant one, it is no longer reasonable to terminate pregnancy when such tumours coincide with pregnancy, or to advise against pregnancy when a malignant melanoma has been adequately treated. The future of any young woman who has had a malignant melanoma is unpredictable; but, while awaiting her turn of the wheel of fortune, she can still bear children with a reasonable assurance that thereby she will not have compromised her chance of ultimate survival.

Vaccination against Poliomyelitis

THE best method of preventing poliomyelitis has long been debated. Until recently, except in Russia, the debate has been mainly academic because supplies of attenuated vaccine made and tested to the stringent requirements of the British and U.S. authorities have not been available. Now, owing largely to the research and enterprise of pharmaceutical firms, a real choice between killed and attenuated poliovaccine can be made. We previously suggested [13] that, for the present at least, there was no need to switch from killed to attenuated vaccine in this country. This view was based on the fact that killed vaccine has been shown repeatedly to be effective against paralytic poliomyelitis, and that claims for better protection by living vaccine are unproven. In this country in 1959 killed vaccine was estimated to be about 80% effective,[14] and in the U.S.A. in the same year over 90%.[15] In Australia and Sweden the offer of killed vaccine in community-sponsored programmes has resulted in high rates of vaccination and a steady decline in incidence of poliomyelitis. In the U.S.A.,[16] Canada,[15] and Israel [17] the vaccine has also proved highly effective; but nevertheless serious outbreaks have occurred mainly because substantial poorly vaccinated subpopulation groups have remained—for example, lower socioeconomic groups in the U.S.A. and the province of Quebec in Canada, and the Arabs in Israel. In this country the number of cases of paralytic poliomyelitis declined steadily after the introduction of killed poliovaccine until this year, when there have been local outbreaks of poliomyelitis mainly in unvaccinated or incompletely vaccinated people. The control of such small outbreaks is discussed by DICK and DANE,[18] who believe that children should be quarantined (a view long held by AGERHOLM [19]) since a chain of infection can often be traced. They favour immediate vaccination of all close and family contacts with highly potent killed vaccine ('Purivax'), which they find produces antibodies in four days in monkeys. Wider circles of immunisation should be carried out with ordinary killed vaccine. Thus the campaign is started as soon as the first case is detected and can be graded according to the needs of the situation. The alternative method of using living vaccine is much more difficult to grade in this way. The decision when to use attenuated vaccine in these circumstances is difficult. Does one case or ten call for such action? Two has been suggested.[20] When it has been decided to use the vaccine this must be employed on a wide scale in the community, to blanket the area. The exact area to be treated may also be a matter for doubt. Should one case in Little Bromwich demand the mass vaccination of the whole of Birmingham?

One of the main attractions of living vaccine is the state of alimentary immunity that develops after infection; but this is not absolute, and GARD [21] has long maintained that such immunity depends on adequate titres of circulating antibody which may be achieved by active immunity, as a result of infection or immunisation, or by passively transmitted antibodies. DICK et al.[22] provide some evidence that a relative resistance to type-1 virus does develop after administration of killed vaccine; and LEPOW et al.[23] found that passively transmitted maternal antibodies limited multiplication of attenuated poliovirus in babies. Living vaccine, however, does achieve a quicker and better alimentary immunity, through viral interference as well as through specific immunity. If, therefore, attenuated vaccine is to be used in an epidemic, it should be administered on a wide scale to create if possible a barrier to the spread of wild poliovirus strains. Such a mass campaign may also be advisable for safety. Many studies have shown that the vaccine virus changes on passage in the human gut to a state of greater virulence than would be acceptable in a

11. George, P. A., Fortner, J. G., Pack, G. T. *Cancer, N.Y.* 1960, **13**, 854.
12. White, L. P., Linden, G., Breslow, L., Harzfeld, L. *J. Amer. med. Ass.* 1961, **177**, 235.
13. *Lancet*, 1960, ii, 531.
14. Geffen, T. J. *Mon. Bull. Min. Hlth Lab. Serv.* 1960, **19**, 196.
15. Salk, J. E. *Lancet*, 1960, ii, 715.
16. Langmuir, A. D. *J. Amer. med. Ass.* 1961, **171**, 840.
17. Melnick, J. L. U.S. Communicable Disease Centre, poliomyelitis surveillance report no. 230, July 21, 1961.
18. Dick, G. W. A., Dane, D. S. *Med. Offr*, 1961, **105**, 369.
19. Agerholm, M. *Lancet*, 1953, ii, 287.
20. See *Brit. med. J.* 1961, i, 1223.
21. Gard, S., Böttiger, M., Lagercrantz, R. First International Conference on Live Poliovirus Vaccines; p. 350. Washington, 1959.
22. Dick, G. W. A., McAlister, J., Briggs, M., Nelson, R., Field, C. M. B. *Brit. med. J.* July 29, 1961, p. 266.
23. Lepow, M. L., Warren, R. J., Gray, N., Ingram, V. G., Robbins, F. C. *New Engl. J. Med.* 1961, **264**, 1071.

virus strain[24 25]; and DANE et al.[24] (contrary to other workers) have produced evidence that this change is progressive at least for Sabin's type 2. They also find that virus is excreted in high titre by those who have received Sabin's vaccine strains. The theoretical danger is that the use of the vaccine in children may lead to the spread of virus to non-immune adults who, being more susceptible, may be paralysed. While no trouble of this sort has so far been experienced after large-scale administration of Sabin strains (which are incorporated in British-made attenuated vaccine), behind the Iron Curtain, and also in Cincinnati,[26] despite adequate surveillance the danger to adults has proved real. This was illustrated by the occurrence of 7 cases of poliomyelitis—5 in adults—in a group who received Cox Cox strains.[27] These considerations undoubtedly weighed with the W.H.O. expert committee[28] when they suggested that extreme care should be taken in the use of attenuated vaccine in countries where over 20% of cases are found in those over the age of 15. In this country the proportion of paralytic cases in patients aged 15 years or over was 34% in 1956 and 30% in 1959.

At present poliomyelitis is coming under control in this country, and regardless of which method of immunisation is chosen it seems likely to follow diphtheria into virtual extinction. The situation does not demand a radical reversal of policy with a new mass campaign. It seems reasonable to persevere with killed vaccine of adequate potency, for then vaccination against poliomyelitis could follow the schedule adopted for other immunisation procedures.[29] The prospects of a quadruple vaccine are good: at present the rate of diphtheria immunisation is unsatisfactory, but a quadruple vaccine should raise this rate because of concern about poliomyelitis. In a few years paralysis due to other enteroviruses may prove more troublesome (already Coxsackie A7 virus has been shown in this country to cause paralysis[30]); and the incorporation of newly emerging pathogenic viruses is likely to be easier in a killed than in a living vaccine.

Androgens in Anæmia

IN 1959 SHAHIDI and DIAMOND[31] reported some success in the treatment of aplastic anæmia in childhood with a combination of androgen and steroid drugs. Aplastic anæmia in adults is serious enough; but remission does occur, and ISRAËLS and WILKINSON[32] were able to report 11 remissions in 45 patients treated with supporting blood-transfusions and prednisolone. In children remissions are far less usual; at Boston Children's Hospital SHAHIDI and DIAMOND found records of 40 patients with aplastic anæmia in twenty years, and spontaneous remission had occurred in only 2; the others died from generalised infection or hæmorrhage. Transfusions, steroids, vitamins, and splenectomy had been tried alone or in combination without success. The use of the androgen, testosterone, was suggested by its observed stimulating effect on red-cell formation in patients under treatment for breast cancer, and also by the observation that in 2 boys with aplastic anæmia spontaneous remission accompanied secondary sexual development. 5 patients (2 boys and 3 girls) were treated; all had complete aplasia with low counts of red cells, granulocytes, and platelets in the blood. Testosterone was given sublingually as propionate or as methyltestosterone, the dose being 1–2 mg. per kg. body-weight daily. The corticosteroid used was triamcinolone 8–12 mg. daily. The results were encouraging; of the 5 patients 4 showed reticulocytosis with a subsequent rise in hæmoglobin; the increase in hæmoglobin was relatively slow to appear—in 3 of the patients one to two months elapsed, and in 1 patient five months. Once the remission appeared, regular transfusion of blood could be stopped. All the patients had improved granulocyte counts, but improvement in the platelet count was irregular. Bone-marrow specimens taken at the height of the remission showed considerable active red-cell formation, whereas previously there had been little.

SHAHIDI and DIAMOND[33] have lately reported results with 24 patients treated during the past two and a half years; in 17 the aplastic anæmia was classified as " acquired ", and in the remaining 7 as " constitutional " because there were inherited abnormalities; 2 of these patients had affected siblings, suggesting that the disease was the Fanconi type of aplastic anæmia. Dosage was similar to that in the earlier series except that when necessary oral methyltestosterone 2 mg. per kg. body-weight was given. In 9 of the patients with acquired aplastic anæmia, chloramphenicol might have been responsible, and 2 had been exposed to dicophane (D.D.T.). After treatment for some months 13 of the 17 patients with acquired aplastic anæmia had a sustained reticulocytosis; 3 relapsed within three to seven months, and 1 died from an unrelated cause. In the 9 successful cases treatment was discontinued when the hæmoglobin reached 12–14 g. per 100 ml.; there was usually sufficient improvement, too, of polymorphs and platelets. When testosterone was withdrawn the hæmoglobin level dropped slowly for about a month, sometimes to 8 g. per 100 ml.; in the second month the level remained steady or began to rise; and in the third month it returned to normal levels. So far none of these patients has relapsed, and periods of three to twenty-two months have passed since treatment was stopped. Side-effects of the testosterone, such as acne, hirsutism, and genital enlargement in the boys, were not troublesome and subsided two to three months after the treatment was stopped. All 7 patients with constitutional aplastic anæmia had a sustained rise of reticulocytes and hæmoglobin in the blood; but when

24. Dane, D. S., Dick, G. W. A., Briggs, M., Nelson, R., McAlister, J., Connolly, J. H., Haire, M., McKeown, F., Field, C. M. B. *Brit. med. J.* July 29, 1961, p. 259.
25. Dane, D. S., Dick, G. W. A., Briggs, M., Nelson, R., McAlister, J., Connolly, J. H., Haire, M., McKeown, F., Field, C. M. B. *ibid.* p. 269.
26. Sabin, A. B., Michaels, R. H., Spigland, I., Pelon, W., Rhim, J. S., Wehr, R. E. *Amer. J. Dis. Child.* 1961, **101**, 546.
27. Erickson, G. M., Flipse, M. E., Menzin, A. W., Clayton, L. B., Markash, R. E., Hardy, A. V. Second International Conference on Live Poliovirus Vaccine, p. 445. Washington, 1960.
28. Expert Committee on Poliomyelitis: third report *Tech. Rep. Wld Hlth Org.* 1960, no. 203, p. 40.
29. Kendall, E. J. C., Miller, A., Tobin, J. O'H. *Brit. med. J.* 1961, i, 176.
30. Grist, N. R. *Lancet* 1960, i, 1054.
31. Shahidi, N. T., Diamond, L. K. *A.M.A. J. Dis. Child.* 1959, **98**, 293.
32. Israëls, M. C. G., Wilkinson, J. F. *Lancet*, 1961, i, 63.
33. Shahidi, N. T., Diamond, L. K. *New Engl. J. Med.* 1961, **264**, 953.

the combined treatment with testosterone and steroid was stopped, they all relapsed quickly and needed further blood-transfusions. They did respond to further treatment, and eventually it became clear that this group of patients need a regular maintenance dose which has to be estimated individually. This may be small—for instance, a 6-year-old boy remains well on 10 mg. of methyltestosterone and 5 mg. of triamcinolone daily. McDONALD [34] in Cape Town applied this treatment to a brother and sister with Fanconi's anæmia; the boy had needed two blood-transfusions in five months, and the girl four transfusions at two-monthly intervals. They were given prednisolone 10 mg. daily, later reduced to 5 mg., and methyltestosterone 2 mg. per kg. body-weight. No further transfusions were needed; six months later they both had hæmoglobin levels over 13 g. per 100 ml., and the bone-marrow activity was regarded as satisfactory.

Another group of patients said to respond to androgen treatment are those with myelosclerosis or myelofibrosis. These patients are usually aged 60 or more; they have a chronic anæmia with often some immature red and white cells in the blood; the liver and spleen are enlarged —the spleen may in fact be very large. Examination of puncture material from the spleen shows that myeloid metaplasia has occurred and that active hæmopoiesis is present. The treatment of such patients is usually limited to blood-transfusions at intervals to prevent the hæmoglobin falling too low; and, since the disease has a very chronic course, this often suffices for a long time. Androgen treatment for this condition was tried by ROSENTHAL and ERF [35] in 1943, and its value was endorsed by KENNEDY and GILBERTSEN [36] in 1957. GARDNER and PRINGLE [37] have given androgens to 9 patients with this disease, in whom the need for supporting blood-transfusions was reduced or even abolished. They used several androgens, including methyltestosterone in daily doses of 50–100 mg., testosterone propionate 100–200 mg. intramuscularly weekly, and testosterone enanthate 400–600 mg. weekly; fluoxymesterone 30 mg. daily by mouth seemed less effective. The treatment was given for periods varying from two to twelve months; in 8 patients the hæmatocrit was clearly improved, and in 7 a definite rise in hæmoglobin was observed, with levels ranging from 11·0 to 15·5 g. per 100 ml.; in 1 patient 18·5 g. per 100 ml. was reached from a starting level of 6 g. When treatment was stopped, relapse to pre-treatment levels ensued in most cases over a period of months, but in 3 the improved hæmoglobin figures were maintained. Side-effects sometimes arose, but as a rule these were not serious. The size of the liver and spleen increased; fluid retention developed in some cases; jaundice appeared in 2 out of 5 patients receiving methyltestosterone, but it disappeared when treatment was stopped; raised blood-uric-acid was found in 8 patients and gouty arthritis in 3 of these. GARDNER and PRINGLE point out that the treatment must be continued for six to eight weeks before it can be decided whether the condition is responding; and they suggest that the response may be poor in patients with little myeloid metaplasia and therefore little erythropoietic tissue to stimulate.

These reports suggest that in two different blood diseases androgens can stimulate blood-cell formation, and that in both treatment with androgens is worth a trial. The treatment must be given for some months before benefit can be expected—an odd finding which does not seem to have been explained. Side-effects must be watched for and controlled. Since we have no really effective treatment either for aplastic anæmia in childhood or for myelosclerosis in the elderly, further work on androgen therapy for these conditions would be welcome.

34. McDonald, R. *Lancet*, 1960, ii, 1146.
35. Rosenthal, N., Erf, L. *Arch. intern. Med.* 1943, **71**, 793.
36. Kennedy, B. J., Gilbertsen, A. S. *New Engl. J. Med.* 1957, **256**, 719.
37. Gardner, F. H., Pringle, J. C., Jr. *ibid.* 1961, **264**, 103.

Annotations

CENTENARY CELEBRATION FOR SIR HENRY HEAD

A CELEBRATION to mark the centenary of the birth of Sir Henry Head, F.R.S., was held at the London Hospital, where he was physician from 1896 to 1919, on Aug. 31. There was a large attendance, including members of the Head family and many neurologists from Britain and overseas. The proceedings consisted of three papers on various aspects of Head's scientific work and a biographical sketch.

Head's remarkable versatility and ability as a research-worker was brought out in a new way by Prof. K. W. Cross in his address on Head's Paradoxical Reflex. Before qualification Head worked in Prague with Hering on problems associated with respiration. Here he introduced new techniques of studying respiration, including the diaphragm slips method of recording respiratory activity, which allowed the first proper recording of the Hering-Breuer reflex, and the use of the cuffed endotracheal tube. Head noticed that, when the vagi had been frozen, inflation of the lungs produced increased respiratory tone. He was at a loss to explain this finding, for it was known that section of the vagi resulted in the disappearance of the Hering-Breuer reflex, and the phenomenon became known as Head's paradoxical reflex. Professor Cross spoke of his own work on the initiation of respiration in the newborn and said he believed Head's reflex might account for the gasping which marks the onset of breathing in the baby. He expressed admiration for Head's creative activity and his own satisfaction that work on the problem which had perplexed Head was taking place in the hospital where he worked for so many years.

Dr. R. A. Henson spoke on Head's Work on Sensation. He began by recalling that Head gave the first account of the effects of positive acceleration on pilots in flight—another of his contributions which had been largely forgotten. Head's important contributions to the subject of sensation are contained in *Studies in Neurology*, published in 1920. His collaborators were Sherren, Thompson, Rivers, and Holmes. Dr. Henson gave a brief summary of Head's views on a peripheral dual afferent system and the general organisation of the sensory system. Tribute was paid to his careful methods of examination and lasting clinical contributions. Head's

insistence on interpreting his findings in terms of evolutionary theory and Jacksonian thought, and his habit of inventing anatomical structures to fulfil his ideas, had rendered him an easy target for criticism, and tended to obscure much that was valuable in his work. However, recent studies on the anatomy and physiology of sensory receptors, and on modality analysis in posterior horn cells, had brought us closer to Head's concept of the organisation of the sensory system, although his idea of a peripheral dual afferent system had not stood the test of time. The researches of Mountcastle and his colleagues at Johns Hopkins on duality in the somatosensory system suggested that Head's speculations on duality might find fulfilment, though in a different way from the one he envisaged; his ideas on the thalamus might prove less wide of the mark than had been supposed. In general it could be said that Head's conception of the afferent system approximated more closely to our own than those of his contemporaries, and that his theories still provided a stimulus to those working on sensation.

Dr. Macdonald Critchley, speaking on Head's Contribution to our Conceptions of Aphasia, said that Head seemed to enter this last field of activity rather hesitantly at a time when the marks of his long and disabling illness were becoming apparent. Before Head the clinical examination of aphasic patients had been haphazard; he introduced a battery of tests which form a landmark in aphasiology. This system of testing was time-consuming and repetitive and took no account of the unusual case. Nevertheless, Head's deep exploration of aphasics had contributed greatly to our knowledge, and much of what we teach we owed to him. His classification was based on his view that aphasia is a defect of symbolic formulation and each variety of aphasia represents a partial disturbance of this function. He recognised four types of aphasia: verbal, nominal, syntactical, and semantic. Although his principles were right his classification was less successful than its predecessors in differentiating clinical types of aphasia and had not replaced them. His approach was functional, and he deprecated precise localisation of speech functions; he seemed uninterested in the problem of dominance. Dr. Critchley concluded that the future study of aphasia demanded the linguistic approach advocated by Head.

Sir Russell Brain spoke on Henry Head, the Man and His Ideas. Head was born in Stoke Newington of Quaker stock. He had always determined to study medicine, and at Charterhouse he was much influenced by his biology master. Before going up to Trinity College, Cambridge, he spent a year learning various scientific techniques in Germany. He qualified at University College Hospital, but in 1894 became medical registrar at the London Hospital, where he was elected to the staff. Head was a born teacher and his enthusiasm was infectious. His interests were wide, embracing literature, art, and music, and he was closely associated with several of the Georgian poets. Sir Russell revealed that after the 1914–18 war Head was approached with a view to his becoming the first professor of medicine at The London, but although he formulated his requirements nothing came of the proposal. Speaking of Head's ideas Sir Russell said that fertile error was preferable to sterile fact, and even in his errors Head had accomplished much by stimulating the thoughts of others.

The proceedings of the meeting will be published in *Brain*.

POSTOPERATIVE DRUG TREATMENT

AFTER operation the patient, who has already been submitted to preoperative medication and anæsthesia, may receive antibiotics; analgesics, sedatives, and tranquillisers; purgatives and enemas; hypotensive or hypertensive agents; anticoagulants; cardiac stimulants or depressants; steroids, diuretics, and bronchodilators; and parenteral blood-volume expanders. To eliminate unnecessary drugs and reduce the use of others would be an act of clemency besides a welcome economy.

Papper et al.[1] demonstrated that analgesics are administered needlessly for postoperative pain, which may often be controlled equally well by placebos.

The investigation was initiated to determine whether the analgesic action of intravenous procaine was exerted through its metabolite, diethylaminoethanol. At the end of each operation, a group of 118 patients received diethylaminoethanol and a control group of 119 patients intravenous saline solution. Postoperative pain was held to be absent if no analgesic drugs were required; moderate if no more than two doses of morphine or pethidine were needed in twenty-four hours, and severe if more than two doses were necessary. There was no significant difference in results between the diethylaminoethanol and saline groups. The investigators were surprised to find that postoperative pain was absent in nearly half, moderate in a third, and severe in less than a quarter of the combined group of 237 patients. Of a further 49 patients complaining of severe pain after hysterectomy, two-thirds were relieved by intravenous saline.

New analgesics, such as phenazocine, are competing with morphine and pethidine. Shaw [2] found that phenazocine did not cause any important blood-pressure changes and it was associated with a pleasant absence of postoperative vomiting, but he criticised its depressant effect on respiration. In a controlled trial, however, Deacock,[3] found that phenazocine and pethidine affected respiration equally. The simple bedside method of estimating the blood pCO_2 introduced by Campbell and Howell,[4] would be useful in assessing the effect of these drugs on respiration.

Some surgeons cover every operation with an umbrella consisting of the antibiotic with the widest spectrum or with the mixture of antibiotics in which they have the greatest confidence. But there is no evidence to recommend prophylactic administration in clean surgery; indeed, such sequelæ as diarrhœa, staphylococcal enterocolitis, and drug resistance strongly contraindicate routine prophylactic administration. For operative chemoprophylaxis surgeons commonly rely on streptomycin, largely because it kills gram-negative organisms which are so liable to contaminate surgical wounds. But the small prophylactic doses often given soon lead to a single-step high level of bacterial resistance, and streptomycin is consequently ineffective. Worse, if administration is continued, notably in the presence of poor renal excretion, labyrinthine function may suffer. Where antibiotic cover is essential, 'Penbritin' [5] may prove a suitable alternative.

The problem of prophylactic anticoagulant administration has been largely resolved by a trial at the Birmingham Accident Hospital.

In this trial Sevitt and Gallagher [6] selected elderly patients with fractured hips, who are particularly prone to venous thrombosis and embolism. A group of 150 patients given phenindione was matched by an equal number not given

1. Papper, E. M., Brodie, B. B., Rovenstine, E. A. *Surgery*, 1952, **32**, 107.
2. Shaw, R. *Brit. med. J.* 1961, i, 825.
3. Deacock, A. R. *ibid.* p. 1465.
4. Campbell, E. J. M., Howell, J. B. L. *ibid.* 1960, i, 458.
5. Rolinson, G. N., Stevens, S. *ibid.* July 22, 1961, p. 191.
6. Sevitt, S., Gallagher, N. G. *Lancet*, 1959, ii, 981.

anticoagulants. Embolism did not occur in any patient receiving adequate anticoagulant therapy; but it was observed in 18% of the control series, and it led to death in 10%. Clinical evidence of venous thrombosis was found in 29% of cases in the control series compared with 3% of the phenindione-treated group. The necropsy evidence was equally striking, for significant thrombosis was found in 83% of 35 patients in the control group who died, compared with 14% of 21 patients in the phenindione group who died.

The present policy in the Birmingham Accident Hospital [7] is to start prophylactic administration of phenindione on the day of admission or the following day in all patients over the age of 45 admitted with fractures of the femur, tibia, or ankle or with severe bruises and burns covering less than 5% of the body-area. Prophylactic anticoagulants are also given to patients with fractures of pelvis and ribs if it is certain that there are no internal injuries which are liable to bleed. Phenindione is continued for about one week after the patient has become ambulant.

The now widespread use of corticosteroids adds a special hazard to modern surgery; for adrenal suppression following their prolonged use contributes to postoperative shock and is associated with an appreciable postoperative mortality. At the Mayo Clinic patients who have had adrenocortical drugs are given intramuscular cortisone acetate in doses of 200 mg. forty-eight, twenty-four, and one to two hours before operation.[8] Short operations may be covered by oral cortisone just before and just after surgery, whereas longer operations may call for supplementary intramuscular prednisolone phosphate or intravenous hydrocortisone hemisuccinate; and, if need be, the latter can be given intravenously during anæsthesia and recovery.

CAROTID-BODY TUMOURS

A CAROTID-BODY tumour usually presents as a symptomless swelling of the carotid triangle in a young or mature adult. In most cases it has been present for a considerable time, and this may suggest lymph-node enlargement due to tuberculous infection or to reticulosis. The diagnosis becomes clear when exploration reveals a highly vascular swelling adherent to the carotid vessels; but the surgeon may well wonder what to do. By and large, experience has shown that operations for carotid-body tumour tend to be more dangerous than the condition itself. The mortality of resection of the carotid bifurcation, even in young patients, is as high as 30%; and without resection removal of the tumour has carried a 15% fatality-rate. Arterial reconstruction seemed to offer a solution, but only a few reports so far exist.[9 10] This operation does not seem to be generally applicable to the cases in which surgery is most needed [11 12]—namely, large tumours in which the upper stump of the internal carotid artery is much too close to the base of the skull to allow manipulation for successful anastomosis by suture.

Is carotid resection ever justified? Only a real suspicion of malignancy, supported by histological evidence, could be sufficient reason for the surgeon to take this grave step. But this evidence itself may be open to question. Other locally malignant and slowly metastasising tumours of the carotid region—for example, some types of thyroid carcinoma—may be hard to distinguish. The incidence of malignant change in true carotid-body tumour has probably been overestimated. Most are benign, and a plane of cleavage can generally be found by a careful and experienced operator, as was shown by Gordon-Taylor over twenty years ago.[13] But there are cases in which the vascularity is such (and this may be suspected from the appearances at angiography before the operation) as to give rise to difficulty, and the surgeon may feel obliged to apply carotid ligatures. In this type of case Jepson and Opit [12] have tried a compromise: with or without temporary carotid occlusion a subcapsular dissection and piecemeal removal of the whole tumour is quickly carried out, the space is packed until the bleeding stops, and the capsule is resutured. These workers recommend subsequent radiotherapy.

We may, then, conclude that a limited operation of some kind should always be preferred in this generally benign disease, and that when in doubt the prudent surgeon will ascertain by biopsy that he is not dealing with some other malignant tumour for which carotid resection would be unjustified.

NOISE IN HOSPITALS

IN the past few years efforts have been made to make the patient's stay in hospital shorter and more pleasant,[14] and much attention has been paid to noise control. King Edward's Hospital Fund for London has published two reports [15] analysing the reactions of hospital patients to different noises, and following these reports the Ministry of Health has circulated a memorandum [16] which publishes a report by the Standing Nursing Advisory Committee of the Central Health Services Council.

Not all patients are distressed by the same noise; but sick people in general are more easily disturbed than those who are well, and hospitals are asked to consider and to act on reports from convalescent patients about distressing noises. The memorandum recommends that each hospital should have its own noise-control subcommittee to deal with these reports. The idea of yet another subcommittee may suggest more noise rather than less; but some means of sifting the complaints and dealing with the noises must be devised, and if such groups could make changes they might prove extremely valuable.

The site of the hospital is of course important—no patient can expect perfect peace in one flanked by a milk depot and backing on to a night club—but within the hospital itself much can be done to influence the amount of noise by careful arrangement of wards for special groups of patients. A recovery ward for those who have undergone operation ensures more peace for the other surgical patients. The noisy senile patients with disturbed sleep rhythm who abound in most orthopædic and general medical wards, and who may require clean bedding twice in a night, could be placed in sound-proof cubicles in hospitals (and they are many) which have no ward for acute geriatric cases. It is notoriously difficult to sleep in an obstetric unit, even for those whose labours are over; and when the labour rooms are at the far end of the main ward, sleep is constantly broken by attendants and students hurrying to the labourers.

The provision of silent or near-silent equipment must often be restricted by lack of money, but in some cases the

7. Sevitt, S. *in* Symposium on Anticoagulant Therapy (edited by Sir George Pickering); p. 249. London, 1961.
8. Paris, J. *Proc. Mayo Clin.* 1961, **36**, 305.
9. Conley, J. J. *Arch. Otolaryng., Chicago*, 1957, **65**, 437.
10. Crile, G., Humphries, A. W. *Amer. J. Surg.* 1957, **94**, 649.
11. Westbury, G. *Brit. J. Surg.* 1960, **47**, 605.
12. Jepson, R. P., Opit, L. J. *Aust. N.Z. J. Surg.* 1961, **30**, 175.
13. Gordon-Taylor, G. *Brit. J. Surg.* 1940, **28**, 163.
14. See *Lancet*, 1961, i, 706.
15. See *ibid.* 1958, ii, 1269.
16. H.M. (61) 68.

quieter is also the cheaper. Piped-in oxygen prevents noise from clanking cylinders, and oxygen is cheaper when bought in bulk. Opaque plastic doors are comparatively cheap and are proof against any attempt to bang them. In some cases, on the other hand, the less noisy equipment is not the most satisfactory from other points of view: curtains round the beds are quieter and more easy to handle than screens, but they tend to harbour more staphylococci. Maintenance is important; but the suggestion that "taps should be well-maintained to ensure that they do not drip" may be hardly relevant, since in many hospitals the dripping tap cannot be heard above the noise of the washing-up in the adjacent kitchen.

Ultimately, the success of efforts to control hospital noise depends on the quality and quantity of the staff. In teaching hospitals it is possible to insist on a much higher standard than at outlying hospitals, where the staff must move twice as quickly to do twice the work, and have less time to remember to close the door while they do the washing-up—even if there is another nurse to watch the patients while they do so.

GREASE-GUN INJURIES

EARLY in 1937 a correspondent in an American medical journal,[1] who was concerned over the possible effect on the body-tissues of diesel oil injected under high pressure, asked for information on the lesions which might result. At that time no instance of such an injury had been reported, but within a few weeks Rees [2] described the case of a motor mechanic who, as he was servicing a diesel engine, actuated the release valve whilst the tip of the fuel injector was about an inch from the tip of his middle finger. Oil, under a pressure of 4000 lb. per sq. in., was blown into the finger through a wound which bled only very slightly, and such severe pain followed that opiates were required for its relief. Necrotic changes developed two days later, and the finger required amputation through its metacarpal.

In the twenty-four years which have since elapsed, hundreds, and perhaps thousands, of oil-injection injuries have been sustained. Sometimes the victims have been diesel engineers, but more often they have been operating the lubricating guns used on cars and aircraft. The disability has varied from the loss of several fingers or crippling fibrosis of an entire hand to the formation of a chronic discharging sinus on a finger-tip. Yet surprisingly few doctors are familiar with the condition, and little has been written about it. Even the latest report, by Stark et al.,[3] brings the total number of cases described in the English language up to only 23.

Diagnosis is not always easy. Several hours may elapse before the injected part becomes painful, and the patient may finish his day's work before presenting with a condition which is likely to be mistaken for an infection unless the relevant history is elicited. Such an error can be disastrous, for the treatment of what is essentially an ischæmic lesion with any form of heat is likely to precipitate gangrene. Wide dissection of the swollen tissues should be carried out under general anæsthesia and in a bloodless field, as an urgent emergency procedure. Small incisions, as Stark et al. point out, are useless; for the injected material spreads widely, and not necessarily along the usual soft-tissue planes. A surprising amount of it is often found at a considerable distance from the entry wound, and it needs to be scraped out with a blunt curette. All damaged non-essential tissue must be excised. Most operators have been tempted to try the effect of ether and similar solvents; but much of the offending grease is in a dispersed particulate form, and, if it is not amenable to scraping, cannot be dissolved either. Fortunately the beneficial effects of operation are sometimes out of all proportion to the amount of material removed, and are then probably ascribable to decompression. Surgery is often still indicated even when two or three weeks have elapsed, though it will then be followed by a lesser improvement.

Besides wider recognition of this condition by doctors, action should be taken, as Harrison [4] has urged, to inform those who use high-pressure lubrication apparatus of the risks. Inquiries at even two or three garages will commonly bring to light a history of at least one instance of an injection injury; and it usually transpires that no-one had ever warned the patient about the danger of using one hand to steady a flexible component (typically a brake cable) while lubricating it with the other. Notices might well be displayed near high-pressure grease-guns urging those who use them to treat them, in Smith's [5] phrase, "with all the precautions applicable to the muzzle of a loaded rifle".

REPORT ON PRISONERS

THE annual report of the Commissioners of Prisons for 1960 [6] records that after a sharp decline in numbers late in 1959, the trend was again upwards, the average prison population during the year being 26,824—1·8% up on the previous year—a figure which reflects the 10% increase in crime for that year.[7] As usual a large number had not been tried (daily average 1400) and, also as usual, some 40% of these were not subsequently received in prison on conviction. As a result of the Street Offences Act, 1959, total convictions for such offences were dramatically reduced, but imprisonment was imposed more than twice as often. Pre-release hostels are burgeoning, with 9 so far and 5 more in preparation; and group counselling is still spreading with apparent success. The scene in general is one of steady unspectacular improvement, apart from recruitment—the numbers of prison officers was virtually unchanged and the officer : prisoner ratio fell from 1 : 5·38 to 1 : 5·5. The physical health of prisoners was well maintained; but of the 260 received under sentence at Wandsworth Prison in July, 1960, no less than 24% were found to have a psychiatric history. This rate was especially high among short-sentence men—the rate for those given over six months was 11%. It is surprising that a declining number of men is thought suitable for psychiatric treatment—only 59 cases completed treatment at Wormwood Scrubs, and 51 received psychotherapy at Wakefield. Psychiatric services in the prison have always been deplorably inadequate. We need to be told at much greater length what types of case receive treatment, how cases are screened and selected, why some are rejected, and what the treatment process consists of.

Prof. M. L. ROSENHEIM and Prof. WILSON SMITH have been appointed members of the Medical Research Council.

1. Feiman, E. M. *J. Amer. med. Ass.* 1937, **108**, 225.
2. Rees, C. E. *ibid.* 1937, **109**, 866.
3. Stark, H. H., Wilson, J. N., Boyes, J. H. *J. Bone Jt Surg.* 1961, **43A**, 485.
4. Harrison, R. *Brit. J. Surg.* 1959, **46**, 514.
5. Smith, F. H. *J. Amer. med. Ass.* 1939, **112**, 907.
6. Report of the Commissioners of Prisons for the year 1960. Cmnd 1467. H.M. Stationery Office. Pp. 195. 9*s.* 6*d.*
7. See *Lancet*, Aug. 26, 1961, p. 472.

Special Articles

THE DISPOSAL OF INFECTED LINEN

K. B. ROGERS
M.D. Lond.

NOEL A. J. SLATER
M.B. Birm.

From the Children's Hospital, Birmingham

DURING a medical students' course at Hamburg, one of us (N. A. J. S.) visited a sanatorium which had a novel way of disposing of infected linen (Bien 1955, 1957, Arzt 1956). The canvas bags used for collecting the linen had one side sewn together with an alginate thread; and, after being filled, they were closed with a strong elastic band round the top. On arriving at the laundry they were thrown into a solution which caused the alginate thread to break and facilitated the removal of adherent proteinous material. After a suitable time, the temperature in the washing machine was raised to 80°C to kill the non-sporing organisms. The linen and the open bags were then laundered, after which the bags were sewn together again with alginate thread.

A committee of the Central Health Services Council (1959) recommended that soiled linen should not be counted in a ward or its annexes but should be immediately placed into a strong washable canvas bag and remain there until it reaches the laundry. The German technique improves on this recommendation, because the soiled linen is not touched until it has been sterilised.

We started our own investigations with alginate thread purchased in Germany; but we later found that the basic alginate yarn had been exported from England by Courtaulds Ltd.; and an English manufactured alginate thread is now available which is much cheaper. The product used for dissolving the thread was called 'Enzyme 1500' by the Germans; but its active ingredients seem to be sodium carbonate and sodium hydroxide. Imperial Chemical Industries' commercial preparation of sodium carbonate 'Soda Ash' has proved equally effective at less than a twentieth of the cost, and it contains no sodium hydroxide.

Thus, though never employed for the purpose described here, both the alginate thread and the essential ingredient for its destruction were already to be had in this country. They have been used for most of our field trial and for many of the laboratory experiments.

DISPOSAL OF SOILED NAPKINS

In our hospital the method has been adapted for the transport of soiled napkins. As our sewing-room could not possibly reconstruct all the bags required, we have used disposable bags:

These are made of gauge-120 British 'Visqueen' polyethylene and are of a size suitable for lining the pedal-action bins (binettes) used for soiled napkins in our hospital's cubicles. Messrs. J. & J. Haling (Plastic Converters) Ltd., 12, Moreton Street, Great Ducie Street, Manchester, 3, supply the bags in a continuous roll which is 15 in. wide: at $17\frac{1}{2}$ in. intervals this is heat-sealed across its width, and perforated just above each sealed section. When an individual bag is required the polyethylene is torn across at the next line of perforations. The bag is inserted into the inner metal can of the binette to provide it with a complete lining and leave about 2 in. of polyethylene to be turned back over the upper edge of the inner can. When enough napkins are in the bag, the nurse raises the turned-over edge and closes the bag with a small elastic band. The closed bags are taken to a container outside the ward and thence to the laundry at intervals during the day.

Enough soda-ash powder (I.C.I.) is added to provide a 1% solution in the first washing-machine, into which the unopened bags are thrown. The temperature of the solution is adjusted to 50°C. Experiment has shown that if fæces are trapped in a napkin which is in the sodium-carbonate solution at or near 100°C the napkin is considerably stained; but at 50°C no staining occurs. In the laboratory also we found that, though the alginate thread broke within 20 seconds at 100°C, it took only $1\frac{1}{2}$ minutes to break at 50°C. With the solution in the washing-machine maintained at 50°C, three-quarters of the bags opened within 3 minutes and all within 5.

After the bags have been in the solution at 50°C for 20 minutes, the temperature is raised and the solution is boiled for 10 minutes. (This has not caused any staining of the napkins, probably because fæcal material is now widely dispersed.) The laundering of the sterilised napkins is completed by the usual processes, which remove all traces of alkali. Examination of the effluent from the first washing-machine showed no live non-sporing organisms. The opened polyethylene bags are not used again when removed from the washing-machine, but they may be saleable as salvage.

Arzt (1956) described how the final sterilisation was carried out at a temperature of 80°C, and Boycott (1959) used a temperature of 82°C to sterilise napkins. But we found no disadvantages when the contents of the washing-machine were boiled, which is simpler for the laundresses than adjusting the temperature to 80°C.

The smell usually associated with the washing of dirty napkins is no longer noticeable in the laundry, probably because the soiled napkins remain sealed in the bags until these break open and allow the napkins to float into the fluid of the *closed* washing-machine.

Now that we have proved the value of this technique for the transport of the "dirtiest available material, soiled napkins from an infants' ward" (Sandiford et al. 1959), we are starting to use the same methods for the transport of other infected linen to the laundry.

When we were investigating the use of the alginate thread, we were introduced to a second technique for closing the bags:

Henkel Leim, made by Henkel of Düsseldorf, is a special paste. It is applied to the edges of the open sides of the canvas bag and these two edges are pressed firmly together; after 2 hours the bag is securely closed and it will withstand all normal stresses and strains. When the bags sealed in this way were received in the laundry, they were thrown into a special solvent solution.

Laboratory experiments showed that if the bag was placed in water the special paste no longer held the sides together: at 7°C the bond broke in 5 minutes, and at 20°C the sides fell apart in under a minute. Hence if bags containing soiled linen were transported through the open and became wet, they could have fallen apart before they reached the laundry.

No further work on this method was done.

THE ALGINATES

Nelson and Cretcher (1929) first described the isolation of alginic acid, and Takahasi (1939) showed how treatment with aluminium sulphate and formalin improved the mechanical properties and water resistance of alginate threads. Soon alginate fibres were used for many purposes in the weaving industry. In medicine, they have been used for hæmostasis (Passe and Blaine 1948, Oliver and Blaine 1950) and for estimating the number of organisms present on various surfaces (Higgins 1950).

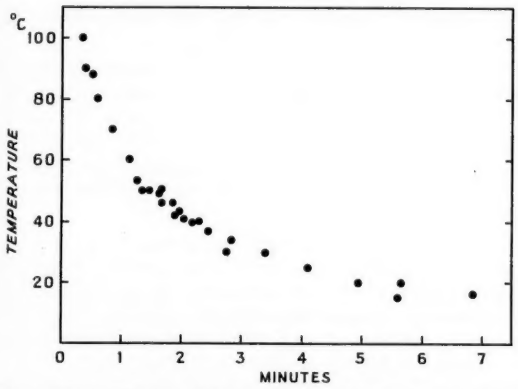


Fig. 1—Time taken for alginate thread to break at various temperatures in 1% sodium-carbonate solution.

Breaking of Alginate Thread

The thread was tested by looping an 8 in. length through a 1/4 Whitworth standard nut (made of mild steel and weighing approximately 3·17 g.), and noting the time taken for the thread to break and the nut to fall when it was hanging freely in the sodium-carbonate solution at various temperatures. The time of breaking varied with the temperature (fig. 1).

When alginate wool (Higgins 1950) is used for the bacterial sampling of surfaces, it is dissolved in sodium hexametaphosphate to liberate the adherent organisms. Solutions of this were too slow for use in the laundry and they would have been much more expensive than soda-ash. All the chemicals we have employed have taken too long to dissolve the thread unless they contained sodium carbonate.

Fig. 2 shows how the individual fibres of the alginate thread swell, loosen and fracture, when placed in the alkaline solution.

Enzyme 1500.—Analyses showed that this consisted of sodium carbonate 43%, sodium hydroxide 36%, sodium chloride 3·5%, and 2 : 4 dichloro–3 : 5 xylenol 1·2%, with a trace of silicone oil and a residue of moisture. At the concentration of the solvent used in the washing-machine the small amount of disinfectant would have been reduced to the ineffective strength of 0·01%.

Soda-ash contains 98·65% sodium carbonate, less than 1% sodium bicarbonate and sodium chloride, and traces of other salts and water-insoluble matter.

Arzt (1956) stated that 1% sodium carbonate did not break down proteins in pus and blood, that it tended to fix precipitates in materials, and that it damaged the textile fibres when used repeatedly. He said that his enzyme

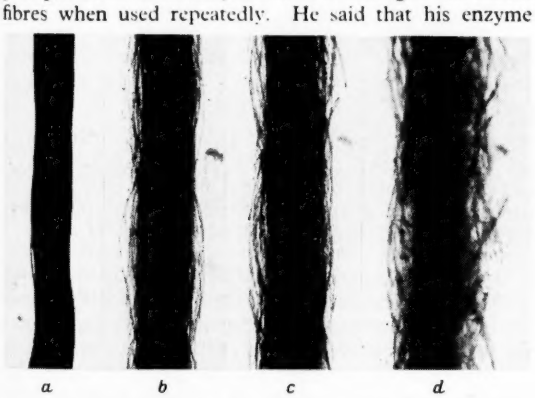


Fig. 2—Photomicrographs of a thread showing how the thread swells, the fibres separate and then fracture when lying in sodium-carbonate solution (×12).

1500, which he referred to as a proteolytic enzyme, caused a breakdown of protein matter within 5 minutes at temperatures between 35° and 40°C. We, however, have found commercial sodium carbonate very efficient, and in the 18 months we have used it we have seen no damage to the textile fibres.

COSTS

When supplied in rolls containing 100 bags the polyethylene bags cost £13 10*s.* per thousand (3·24*d.* each). In rolls of 1000 they cost £12 per thousand (2·9*d.* each).

In Birmingham, ' Soda Ash ' (I.C.I.) costs £14 17*s.* 6*d.* a ton (1·6*d.* per lb.), or 25*s.* per cwt. (2·2*d.* per lb.).

Alginate thread suitable for sewing through canvas costs £2 7*s.* per lb.

SUMMARY

Dirty linen is collected in bags sewn on one side with an alginate thread. When the bags are placed in a hot alkaline solution in a washing-machine, the thread dissolves, and the linen falls out. It is then boiled in the alkaline solution to kill all non-sporing organisms.

Disposable polyethylene bags have proved very satisfactory for the transport of soiled napkins.

With this technique there is no longer any " handling " of infected linen, since the linen is sterilised before it is touched.

We are indebted to the nursing and administrative staff of the hospital, and in particular to Mrs. Mills and her staff in the hospital laundry, for their cooperation in the evolution of our technique: to Mr. E. J. Billington, group laundry manager, and Mr. I. J. Roxborough of Courtauld's for introducing new products for the trial; to Dr. H. Kohler for his help with translation; and to Dr. A. H. Cameron for the photographs used in fig. 2.

REFERENCES

Arzt, G. H. (1956) *Desinfektion und Gesundheitswesen.* **48**, 33.
Bien, F. (1955) *Krankenhaus* no. 12.
— (1957) *Anstalts Umschau* no. 3.
Boycott, J. A. (1959) *Mon. Bull. Min. Hlth Lab. Serv.* **18**, 115.
Central Health Services Council (1959). Report of Committee on Hospital Laundry Arrangements. H.M. Stationery Office.
Higgins, M. (1950) *Mon. Bull. Min. Hlth Lab. Serv.* **9**, 52.
Nelson, W. L., Cretcher, L. H. (1929) *J. Amer. chem. Soc.* **51**, 1914.
Oliver, L. C., Blaine, G. (1950) *Brit. J. Surg.* **37**, 307.
Passe, E. R. G., Blaine, G. (1948) *Lancet*, ii, 651.
Sandiford, B. R., Blowers, R., Mitchell, E. R. (1959) *Mon. Bull. Min. Hlth Lab. Serv.* **18**, 110.
Takahasi, T. (1939) *Rayon World* (Japan) **7**, 11.

EMPLOYABILITY OF LONG-STAY SCHIZOPHRENIC PATIENTS

W. V. WADSWORTH
B.Sc., M.B. Manc., M.R.C.P., D.P.M.
MEDICAL SUPERINTENDENT

R. F. SCOTT
B.A. Lond., Dip. Psych.
INDUSTRIAL DIRECTOR

B. W. P. WELLS
B.A. Bristol
RESEARCH PSYCHOLOGIST

CHEADLE ROYAL HOSPITAL, CHESHIRE

To determine how far long-stay psychotic patients can meet the demands of ordinary employment we decided to compare their performance with that of a group of normal workers.

12 schizophrenic patients were selected, who had been in hospital from 3 to 43 years (average 17 years)—who had never before worked in a sheltered workshop. 12 normal workers were recruited through advertisements and interviews. All 24 were given half an hour's training in the task chosen (gluing the edge of a cardboard hat-shape and affixing a piece of crepe paper). Patients and normals were paid the same fixed price per

piece. They worked in a large room which was divided down the middle by a screen.

There were 3 observers in each division, and the following observations are based on their records of the output, behaviour, and reactions of the two groups. The investigation lasted eight weeks.

PERFORMANCE

The efficiency of the patients over the whole period, when measured against the normals, was 35·4%. They were 49% as efficient on the first day of the study, but their rate of increase over the eight weeks was relatively slower, the normals improving their production to 309% and the patients to 250%. The rate of increase for the patients was steady and was still improving when, after six weeks, the first part of the study ended. The normals, on the other hand, seemed to have reached their maximum by the thirty-third day and after that ceased to show a steady increment.

Wastage of Material and Time

Considered as a percentage of their saleable work, wastage was 3·0% compared with 1·8% for the normals. The normals wasted only 3 minutes in nearly 960 man-hours, and the patients 30½ hours, but of this 24 hours was due to 2 patients. The normals needed only 25 minutes of the supervisor's time in solving work problems, the patients 2 hours and 57 minutes.

Behaviour

No incident occurred when the help of a doctor or nurse was needed. Some patients had to be accompanied to the water-closet to make sure that they did not wander or reappear incompletely dressed. None of the behaviour recorded was disabling though the individual patient might be regarded as " odd ".

Fatigue

Fatigue was measured in terms of variation in performance from one quarter-hour period to the next over the 2-hour work session. The patients did not show the dramatic fatigue often ascribed to chronic schizophrenics despite earlier beliefs that they could only be effective over short periods—i.e., an hour or less.

INCENTIVES

At the end of the sixth week incentives were introduced. The patients reacted more sensitively to incentives than the normals, who were probably already working almost to capacity. The following three types of incentive were tried:

Social appeal.—The supervisor appealed to the groups for higher production for three days on the grounds that the unit had more orders than it could meet. Production for these three days was increased on that for the previous three days by 7% for patients and 5% for normals. This result tends to support the hypothesis that schizophrenic patients are capable of a limited amount of realistic adjustment to social demands.

Knowledge of work performance.—A histogram showing his performance over the three previous days was attached to each worker's table and amended each day. The response to knowledge of results was 4% increase for patients and 2% for normals over the previous two days' production.

Increased pay.—The supervisor announced that for two days it had been decided that instead of being paid at the rate of 1*d.* per piece they would be paid 1½*d.* The performance of both groups declined, perhaps because they felt that this rather obvious incentive suggested that they were not thought to be working to their full ability.

A comparison of the behaviour of the patients during weeks 1–6 (without incentives) with weeks 7–8 (with incentives) showed improvement on the following points:

	Demands on supervisor's time	*Idleness*	*Abnormal behaviour*	*Visits to W.C.*	*Other Absences*
Decreased by ..	91%	33%	65%	30%	100%

During the first six weeks the conditions of work were, in a sense, passive because there was no attempt to get the patients to work harder. When incentives were introduced the response to higher demands was both higher production and a better standard of behaviour, suggesting the therapeutic value of demanding situations.

ASSIMILATION

At this stage of the investigation the patients and normals, who had been sitting on different sides of the screen, were mixed and seated alternately. The work of the patients increased by 12% and that of the normals fell by 3%. This may have been because the patients felt that they were regarded highly enough to be allowed to work with the normals, and that they were able to observe and emulate the better work methods of the normals. It is well known to social and industrial psychologists that if individuals or groups are allowed to establish norms and then integrated, the norms will tend to shift towards each other. These shifts are influenced by the numerical supremacy or higher prestige of one of the groups. The shifts in our groups followed this pattern. The relative improvement of the patients was much greater than the relative deterioration of the normals, probably because the normals were both a majority and a higher prestige group.

A number of rank order correlations were made to establish the relationship of some variables to work performance. The group mean I.Q. for the patients was 98·8 and for the normals 101·1. The correlations made were intra-group ones and not between the two groups, as there was no overlap in the performance-variable of the groups and therefore no correlation between groups could exist.

For the patients, there was a significant correlation between I.Q. and performance; and initial performance was significantly correlated with ultimate performance, for both patients and normals. There was no correlation between the performance of the patients and the length of stay in hospital.

The total number of behaviour incidents recorded for each patient was then correlated with a number of other variables—i.e., period in hospital, age, performance, and I.Q. None of these factors were significantly correlated. Correlations based on this and similar tasks may be useful in devising a system of selection and placement within the rehabilitation unit.

DISCUSSION

This study has made it possible to form some estimate of the relative efficiency of our patients. The true comparison should be with the best of the normals rather than with the group as a whole, for a normal industrial piece-rate would be fixed to provide a reasonable rate only for workers who were capable of producing a profit. The pay-packet would act as a selection technique, because poor

producers would leave to look for other jobs. With the patients one is not able to be selective, one must use what one has, so they form a true comparison group. Taking the top 5 normal workers as representing the industrial norm, then the patients were 28·8% as efficient as their normal counterpart. Our results make it possible to establish a pay-scale, based on production, which will yield an economically realistic pay-packet.

CONCLUSIONS

A group of schizophrenic patients, despite the general belief that they live a life divorced from reality, responded to various normal incentives to work. This inquiry supports the view that chronic schizophrenic patients can adjust themselves to reality.

The behaviour of the patients never distressed the normal workers. Indeed it became more and more apparent how little medical or nursing supervision is needed during the patients' working day.

The patients did not show the fatigue so often ascribed to chronic schizophrenics, which contradicts the belief that they can work effectively for only short periods.

The investigation showed that a patient's production is closely related to intelligence—e.g., the most intelligent patients, irrespective of length of illness or symptoms, were the best workers. The response to incentives suggested that the patients, unlike the normals, still had a high potential of improvement after sixty hours of practice. This suggests that the training period, to reach peak performance, is longer for patients, and that incentives may be required to produce or sustain such improvements.

The Nuffield Provincial Hospitals Trust have made a grant in connection with this work.

Points of View

TRAINING IN MYCOLOGY

THE mycoses of man are receiving more attention than ever before. Ringworm and moniliasis, though still common, are now overshadowed in some countries by the systemic mycoses. In the United States possibly a fifth of the population has been infected by *Histoplasma capsulatum*, and the number of new infections (mostly subclinical) may approach half a million a year [1]; while in certain arid regions of that country several million people are carrying for life the serological markers denoting recovery from coccidioidomycosis.[2] Histoplasmosis has been recorded in more than twenty countries, including Britain (where it is a rarity, in others it is also endemic and widespread), while cryptococcosis [3] is now recognised so often in all parts of the world that individual cases rarely merit public record.

Since 1945 the increased world interest in mycoses has had repercussions in this country. There are now a Mycological Reference Laboratory within the Public Health Laboratory Service, and a National Collection of Fungi Pathogenic to Man and Animals. The Medical Research Council has a standing advisory committee on medical mycology (a committee on which the veterinary interests of the Agricultural Research Council are also represented); and the Commonwealth Mycological Institute at Kew, in collaboration with the Bureau of Hygiene and Tropical Medicine and the Commonwealth Bureau of Animal Health, surveys the world literature in the quarterly *Review of Medical and Veterinary Mycology*. In addition, half a dozen or so new posts for medical mycologists have been established in the United Kingdom. The research facilities, if thinly spread, are probably adequate but one serious deficiency is the continuing lack of facilities for instruction in medical mycology.

There may be no major endemic systemic mycosis of man in this country; but, even excluding ringworm, mycotic infections are far from uncommon. Fatal cases of moniliasis (sometimes the sequel of antibiotic therapy) occur, and pulmonary aspergillosis is proving not unimportant [4]; while cases of exotic mycotic diseases are likely to be introduced with increasing frequency. Already at Charing Cross Hospital instances of histoplasmosis, African histoplasmosis, coccidioidomycosis, North American blastomycosis, South American blastomycosis, rhinoporidiosis, chromoblastomycosis, and mycetoma have been recorded by Symmers.[5] Similar cases must be missed by less perceptive pathologists. Furthermore, many medical students and postgraduates come here for training and return to countries where major mycotic infections are prevalent. Most of them must go elsewhere for adequate formal instruction in mycology. That action is needed seems clear. What might be done?

Models are available. At Duke University, North Carolina (the home of the invaluable *Manual of Clinical Mycology* [6]), there has for many years now been an annual summer course on all aspects of medical mycology —a course which has been attended by workers both from this country and from the Commonwealth. Every autumn the medical mycological unit at the Institut Pasteur in Paris organises a month's course of lectures and practical work on medical mycology (in order to attend this year's course one overseas visitor to Britain learnt French). Similar courses are run at other centres in the United States, and there are several comprehensive departments of medical mycology in South American universities; but there is nothing comparable in the Commonwealth. In Britain the only regular courses are the lectures and the short annual course arranged for pathologists and dermatologists by the Institute of Dermatology at St. John's Hospital for Diseases of the Skin, and the little mycology introduced into various courses for diplomas in bacteriology or tropical medicine.

There is now enough sound medical mycological knowledge in this country to bring together a group of mycologists and doctors in order to provide authoritative short courses similar to those organised elsewhere. But such courses need to be based on a vigorous medical mycological unit, such as those at Duke University and in Paris; and nowhere in the British Isles has medical mycology been given departmental status, nowhere has the subject had sufficient long-term security or sufficient backing to enable a teaching and research unit to accumulate experience, material, and literature.

What is the specification for a medical mycological teaching-centre? First one or more mycologists. Mycology is so wide a subject as to be an alternative rather than a supplement to a medical qualification—a lesson we have

1. Puckett, T. F. *in* Histoplasmosis (edited by H. C. Sweany); p. 311. Springfield, Ill., 1960.
2. Fiese, M. J. Coccidioidomycosis. Springfield, Ill., 1958.
3. Littman, M. L., Zimmerman. O. E., Cryptococcosis. New York, 1956.
4. Riddell, R. W., Stewart, G. T. Fungous Diseases and Their Treatment. London, 1958.
5. Symmers, W. St. C. *Trans. R. Soc. trop. Med. Hyg.* 1961, **55**, 201.
6. Conant, N. F., Smith, D. T., Baker, R. D., Callaway, J. L., Martin, D. S.

already learnt from other countries. To the mycologist there must be a medical counterpart—a pathologist for preference. This partnership needs modest technical support, and many of the facilities found in a standard department of bacteriology. Contacts with clinicians (especially those specialising in dermatology and tropical medicine) must be ensured, and liaison with the veterinary profession not forgotten. In other countries some of the medical mycology units which offer instructional courses have diagnostic or other advisory duties, some have not. Most have, and all should have, resources for postgraduates to study for higher degrees and research. (That there should be opportunity for research by the permanent staff goes without saying.)

The medical undergraduate curriculum is already overcrowded, and on the wide view mycoses have not the importance for detailed treatment at that stage. What seems to be most needed is the offer of recurring courses to introduce mycologists or medical graduates or others to the study of medical mycology—courses that any suitably qualified person could take because interested or for any other reason, courses that could be biased for mycologists, the medically qualified, or laboratory assistants, and even for some specialised topics within such general groupings. This is not the place to suggest details of the courses themselves. One generalisation is that little effective training can be accomplished in under a month or six weeks, and another that lectures should take second place to comprehensively planned demonstrations and practical classes.

If any one medical school decided to give medical mycology the attention it merits and to meet the demand which is there, a service to graduates of other medical schools in the country should be envisaged. Perhaps arrangements for medical mycology could be included in the proposals announced by the Minister of Health for regrouping London's postgraduate teaching hospitals.[7] If so, it is not too early to plan for such a development.

G. C. AINSWORTH

7. See *Lancet*, July 1, 1961, pp. 34, 57.

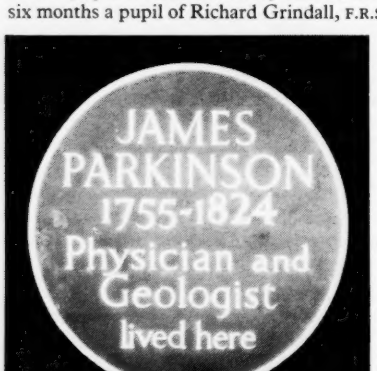
Before Our Time

JAMES PARKINSON AND WILLIAM J. LITTLE

LAST week saw the unveiling of plaques erected on London houses to commemorate London Hospital men whose names are widely known through the diseases called after them. Parkinson's disease was described 144 years ago and Little's disease exactly 100 years ago.

JAMES PARKINSON (1755–1824)

James Parkinson was the son of John Parkinson, a doctor living at 1, Hoxton Square, Shoreditch, then a residential district with lovely gardens. A search of London Hospital records, by Dr. Arthur Morris,[1] has shown that James was for six months a pupil of Richard Grindall, F.R.S., assistant surgeon to The London, after which he practised as a family doctor in his father's house at Hoxton Square. He was a pupil also of John Hunter. He is remembered today for his classic description which came out in his *Essay on the Shaking Palsy* in 1817.



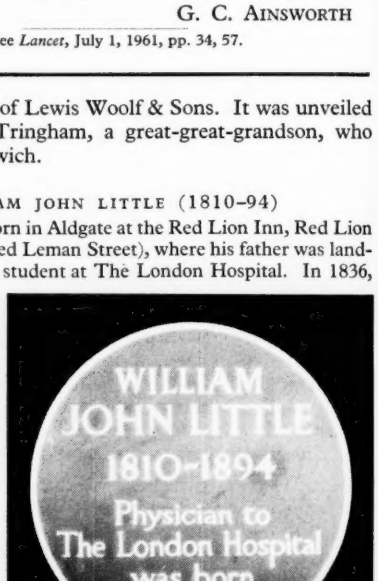
Parkinson was a radical, a reformer, a political agitator, and pamphleteer, and as a member of a secret society (the London Corresponding Society) he got into trouble with Authority. His most important contributions outside medicine are his works on fossil remains and especially his book *Organic Remains of a Former World* (1804) in three volumes. Many fossils are called after him, for example *Parkinsonia parkinsoni*, which is a species of ammonite. His main contribution to geology sprang from his wide reading and many personal contacts; for his particular gift was the collation of information.

The home in which Parkinson was born was demolished some forty years ago, and the plaque appears on the furniture factory of Lewis Woolf & Sons. It was unveiled by Dr. Robert Tringham, a great-great-grandson, who practises in Norwich.

1. *Lancet*, 1955, i, 760.

WILLIAM JOHN LITTLE (1810–94)

Dr. Little was born in Aldgate at the Red Lion Inn, Red Lion Street (later renamed Leman Street), where his father was landlord, and he was a student at The London Hospital. In 1836, stimulated by an interest in his own deformity, he visited Hanover to inquire into the value of Stromeyer's claims for subcutaneous tenotomy. He saw Stromeyer's work and was apparently operated on by Stromeyer for his talipes equinovarus. The result was satisfactory and Little wrote an M.D. thesis for Berlin on talipes. This was the first monograph on tenotomy ever published. In 1839 Little became assistant physician to The London Hospital. His most famous work, *On the Deformities of the Human Frame*, was published in 1853.



A hundred years ago, in 1861, his paper " On the Influence of Abnormal Parturition, Difficult Labours, Premature Birth, Asphyxia Neonatorum, on the Mental and Physical Condition of the Child, especially in Relation to Deformities " appeared in the *Transactions* of the Obstetrical Society of London. This was the first investigation into the cause of spastic rigidity of the limbs of newborn children. It led to the use all over the world of the term Little's disease or spastic diplegia for a group of disabilities beginning at birth. Little became the founder of British orthopædic surgery and established the first orthopædic hospital for the study and treatment of disabilities of the limbs and spine. The Orthopædic Infirmary was opened in Bloomsbury Square in 1840.

The plaque appears on the Old Red Lion, a building of later date. The unveiling was performed by the senior member of the Little family, his grandson, Admiral Sir Charles Little, G.C.B.

D. H.

In England Now

A Running Commentary by Peripatetic Correspondents

I WAS glad to see from your advertisement columns that Baxter has qualified at last. A search through our medical library shows (as accurately as our broken series allow) that it is over four years since he first appeared on those hard lecture-theatre benches, presumably in his third or fourth year. Three years later he was still there, asking the same questions about insulin, and getting the same amused reaction from the lecturer and the rest of the class, who, strangely enough, hadn't changed much either. The blonde, I noticed, was still sitting next to him, smiling gently at his questions. But a few months later he appeared as a houseman, so perhaps the last few sessions in the lecture theatre were only pre-finals tutorials.

But I think Baxter still has rough passages ahead of him in his medical career. His boss's unfortunate advice to "ask Sister about the older forms of insulin" has served only to remind her (judging by the expression on her face) that she will never see thirty again. Baxter will probably have to take her to the pictures to smooth things out.

* * *

One of my more extraordinary experiences was a 1000-mile drive from Chicago to Montreal with three splendid Greek doctors. Nick and George, like me, were heading for an international congress but Savas was just going to stay with his people. They had reached that confident and eccentric stage in which they were thoroughly American but still very obviously Greek, and cross-cultural difficulties were arising vis-à-vis the older generation who clung more firmly to the traditional ways. Accord between us developed with such speed that by the second day out it was possible to mention Cyprus, and we were pretty soon taking photos of each other in various combinations posed in positions of martial dignity grouped around the Greek flag which they displayed proudly on the rear of the car (a British one, incidentally). Customs formalities at the point where we crossed the frontier are usually not onerous, and it took some time for the officer to push from his mind the image of four local day-trippers and grapple with the complexities of my colleagues' varying states of naturalisation or partial tolerance and my own state of vaccination. We had them so worried they sent for the boss and started going through our bags—an almost unprecedented event at that place.

Once in the Commonwealth my colleagues settled down pretty well, but they were greatly shocked when at the theatre the audience rose and sang the National Anthem. They went on about it for days. Later (as a small token of &c., &c.) I sent them the recording of Flanders and Swann including Donald Swann's magnificent little solo in modern Greek (which they declared perfect). They replied in touching terms, but asked why the record had not ended with the National Anthem. They had expected it all through.

* * *

D. M. Jackson tantalised the mess in his fascinating article on nomenclature last week by referring to a word which he would retain at all costs, and which "is the basis of at least one admirable limerick". After some debate we concluded it had not been quoted because the author properly felt that light verse was out of place in a serious article. The Pathologist was quite sure about this, for if it had been the other kind of limerick he would have heard it already. The mess was on its mettle, and many attempts were made over the weekend. The only one which was fit to print is not quite *Golden Treasury* standard, but for what it is worth we offer it to other readers who also felt frustrated.

"*Dysdiadochokinesis*"
Would make a good PH.D. thesis.
The subject's abstruse,
And not of much use,
But it polysyllabicly pleases.

Letters to the Editor

ABDOMINAL MANIFESTATIONS OF ADENOVIRUS INFECTION IN INFANTS

SIR,—Adenovirus was isolated for the first time by Rowe and Huebner [1] from infants with respiratory-tract infections. The virus has also been demonstrated in the intestinal tract: it was isolated [1–3] from diseased mesenteric lymph-nodes and it has been found in inflamed appendices. In upper respiratory infections [4] it is easier to isolate the virus from the stools than from throat smears.

We read the preliminary communication by Mr. Ross and Mr. Potter [5] with much interest, since in November, 1959, we presented the following cases with the clinical symptoms of intussusception and mesenteric lymphadenitis due to adenovirus infection to the Dutch College of Surgeons.[6]

CASE 1.—An 18-month-old girl was admitted because of attacks of abdominal colic. 3 weeks before admission she had had a short attack of diarrhœa and vomiting, which subsided without treatment. A few days before admission she had what seemed to be a common cold. While she was being examined she showed the typical picture of abdominal colic. In the right upper quadrant a solid tumour was felt, approximately 8 cm. long. The temperature was 101·4°F. Rectal examination was negative. The diagnosis was intussusception, and the child was prepared for laparotomy. Shortly before the anæsthetic was given the tumour seemed much smaller, but it was decided to continue with the operation. The small and large bowels looked normal, but in the mesentery several enlarged lymph-nodes were found, some measuring $4\times2\times2$ cm. The largest concentration of these glands was found in the ileocæcal angle. One of the glands and the appendix were removed. Post-operatively the child did very well without further treatment. Microscopical examination of the removed specimen showed enormous hyperplasia of the lymph follicles. Serological tests for adenovirus infection were carried out at the virological laboratory of the University of Amsterdam. The complement-fixation test on the 6th postoperative day was adenovirus type 2 1:128++, type 4 nil, neutralising antibodies nil. On the 15th postoperative day: type 2 1:128++++, type 4 1:1024+++, neutralising antibodies 1:16. Adenovirus type 1 was isolated from the stools.

CASE 2.—A 17-month-old girl was admitted with attacks of abdominal pain for 3 weeks. The day before admission the pain became more severe and colicky, and she vomited. There was no rectal bleeding. The temperature on admission was 101·6°F. While examining the child a mass could doubtfully be felt in the upper right abdomen. A barium enema showed typical ileocæcal intussusception. Elevation of the barium container did not seem to reduce the intussusception. At laparotomy no trace of ileocæcal intussusception was found, but in the terminal loop of the ileum two easily reducible intussusceptions were discovered. A striking finding was an extensive mesenteric lymphadenitis. Except for a short bout of pneumonia, the postoperative course was uneventful. The serological findings were: 5th day, complement-fixation test negative, neutralising antibodies 1:32; 150th day, complement-fixation test negative, neutralising antibodies 1:64. At no time were antibodies found against the patient's own virus, which was isolated from the stools. This virus was identified as adenovirus, not belonging to groups 1–7.

CASE 3.—A 3-month-old boy was admitted because of attacks of abdominal pain for 4 days. He vomited frequently and lost blood in the stools on the day of admission. He was

1. Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., Ward, T. H. *Proc. Soc. exp. Biol., N.Y.* 1953, **84**, 570.
2. Kjellen, L. *Arch. Virusforschung*, 1956, **6**, 45.
3. Veen, J. van der, Ploeg, G. C. van der. *Ned. Tijdschr. Geneesk.* 1958, **102**, 1948.
4. Ploeg, G. C. van der. Thesis, University of Nijmegen, 1959.
5. Ross, J. G., Potter, C. W. *Lancet*, 1961, i, 81.
6. Rutten, A. P. M., Oudejans, E. *Ned. Tijdschr. Geneesk.* 1960, **104**, 2383.

pale and the abdomen was much distended. X-rays showed obstruction of the small bowel. At laparotomy an irreducible ileocæcal intussusception was found. There was also malrotation and severe mesenteric lymphadenitis. Part of the small intestine was gangrenous and had to be removed. A few days later reoperation was necessary because of leakage of the anastomosis. Convalescence was slow but satisfactory. Adenovirus group 5 was cultured from one of the removed glands. No complement-fixating antibodies were present in the serum on the 30th postoperative day. The titre of the neutralising antibodies was 1: 80 on the same day.

Many infants are very poor producers of antibodies, and it is often impossible to demonstrate complement-fixating antibodies in infants at the time of the infection. In 4 out of 7 cases described by Van der Ploeg,[4] where adenovirus was isolated, no complement-fixating antibodies could be demonstrated.

Laurence [7] observed 16 cases of intussusception among 100 patients with mesenteric lymphadenitis. Strang [8] found mesenteric lymphadenitis in 46% of 400 cases of intussusception. Courty [9 10] and Langeron [11] described 4 patients with intussusception, probably caused by severe mesenteric lymphadenitis. "A direct relation is seen to exist between the quantities of lymphoid tissue in the last few inches of ileum and the age incidence of ileocolic intussusception." [12]

Hypertrophy of the plaques of Peyer in the intestinal wall, being part of more or less generalised lymphoid hyperplasia, may well be an important factor in the development of intestinal intussusception.[13 14] Increase in peristalsis, as in simple gastroenteritis, has also been observed in adenovirus infection of the upper respiratory tract [4] and may cause intussusception.

In the past year we have seen 6 other cases of intussusception in 2 of which cultures from the mesenteric lymph-nodes and the stools were positive for adenovirus. Furthermore, 1 of these patients had an elder brother who was admitted to another hospital one month earlier with similar symptoms, which subsided without operative treatment. Adenovirus type-1 was isolated from both these last cases.

Whether the intussusception in case 3 was caused by the adenitis or by an accompanying gastroenteritis does not seem important, for we only want to stress that adenovirus infection in infants may cause serious abdominal conditions, even amounting to irreducible intussusception, requiring resection.

We gratefully acknowledge the help of Dr. F. Dekking, virologist, University of Amsterdam.

Onze Lieve Vrouwe Gasthuis, Amsterdam.

A. RUTTEN
E. OUDEJANS.

MANAGEMENT EFFICIENCY IN THE HEALTH SERVICE

SIR,—Dr. Seale's article of Aug. 20 is more than timely.

The expertise of management is still often regarded as inferior to other professional skills, when in fact it is the function upon which, in a modern society, the effective use of other skills depends. Since the tradition has been that leaders' breed their own successors, the Government-controlled services are led at most levels of management by traditionalists. If ever there was a need for a bureaucratic iconoclast, the need is now. Thank goodness some, but unfortunately not all, of our industries have broken away from this tradition.

While agreeing with Dr. Seale generally, the principles of management he mentions are more often stated:

(1) Unity of command (at the top and within groups).
(2) Reasonable span of control (as many functions to handle as experience and experiment have shown reasonable—usually 7).
(3) Rational assignment (assignation of functions in related groups).
(4) Delegation of authority.

The functions are:

Planning.
Organising.
Controlling.
Commanding.
Coordination.

Each one of these functions in a complex organisation requires, of course, first-class highly skilled managers. Without these, no improvement can be expected. (The Government has belatedly recognised this in the Railways.)

Dr. Seale's estimate of the future is admirable. Like all intelligent proposals it is based on present facts. The prospect without a complete reorganisation is quite dismal for both patients and profession.

The major difficulty is that as a nation we have very few top-rate managers. Their cost is high, but they are worth ten times as much in results.

Dr. Seale's is the most important article published in your learned journal in years; its recommendations should be shouted from the hospital-tops into the ears of our rulers until the National Health Service is a meaningful title.

Dibden Purlieu, Hants.

G. MATTHEWS.

SIR,—The paper by Dr. Seale is very interesting in many respects, especially where he directs attention to the total lack of data on the *quality* of medical care provided in the hospital service. In this connection one is reminded of a paragraph in the Ministry's circular H.M. (53) 87 on medical committees which reads as follows:

"Another function which is not at present usually exercised by such committees but which the Minister thinks would, if exercised, produce results of the *greatest value*, is the systematic review and analysis of the clinical work of the staff. If the results of the work of all departments were regularly reviewed and where practicable subjected to statistical analysis and brought before the full committee at its periodical meetings, discussion of the results would, in the Minister's view, assist all the staff in achieving and maintaining a high standard of clinical work."

One wonders whether this advice has been acted upon at all.

Addiscombe.

A. JOHN TASKER.

BIOCHEMICAL ABBREVIATIONS

SIR,—The use of the initials of chemical names and prefixes to provide convenient abbreviations has been hallowed by tradition. A.T.P., D.N.A., E.D.T.A., 5-H.I.A.A., &c., are generally accepted and useful means of expressing long cumbersome chemical names and have the merit of being correct. Some of the more recently introduced abbreviations, however, do not have this virtue and, as one who has had occasion to use new combinations of initials, may I plead for care to be exercised to ensure that correct ones are used.

V.M.A., for example, is widely but erroneously used to represent 4-hydroxy-3-methoxymandelic acid, the predominant metabolite of adrenaline and noradrenaline found in urine. Why V.M.A. rather than H.M.M.A.? Presumably because of the similarity between the compound in question and vanillin or vanillic acid, but this substance certainly cannot be described as vanillylmandelic acid, which, according to my reckoning, would be α-(4-hydroxy-3-methoxybenzoyloxy)phenylacetic

7. Laurence, A. Quoted by Courty, refs. 9 and 10.
8. Strang, R. *Brit. J. Surg.* 1959, **46**, 484.
9. Courty, L. *J. Sci. med. Lille*, 1955, **73**, 317.
10. Courty, L. *ibid.* 1957, **75**, 572.
11. Langeron, P. *ibid.* 1958, **76**, 470.
12. Perrin and Lindsay. Quoted by O'Sullivan, ref. 14.
13. Roviralta, E., Roca de Viñals, F. *Rev. clin. esp.* 1958, **71**, 45.
14. O'Sullivan, W. D., Child, C. G., III. *J. Pediat.* 1951, **38**, 320.

acid. If it is desired to indicate its resemblance to vanillic acid why not use the perfectly correct, though possibly slightly old-fashioned, α-hydroxyhomovanillic acid (abbreviation H.H.V.A.)?

The name "3-methoxy-4-hydroxymandelic acid" and the corresponding abbreviation M.H.M.A. have appeared in the literature. While the latter is better than V.M.A., it does not conform to the almost universally accepted convention of placing chemical prefixes in alphabetical order.

But, whichever abbreviation is employed, I trust that biochemists, endocrinologists, clinicians, and all others concerned will abandon V.M.A. until someone isolates a compound to which these initials may legitimately be applied.

Westminster Medical School,
London, S.W.1. J. H. WILKINSON.

DRUG-INDUCED GASTROINTESTINAL BLEEDING

SIR,—Recently, while looking for references to amyloidosis in typhoid fever, I came across the following, written in the 1905 edition of Allbutt's *System of Medicine* by Prof. Julius Dreschfeld of Manchester. He says [1]:

"Salicylate of sodium (15–30 grains) was formerly given largely in enteric fever. At the Monsall Fever Hospital some years ago the late Dr. Tomkins, then resident medical officer, tried salicylate of sodium in a very large number of cases; but the depressing effects, the unpleasant accidents (such as delirium, vomiting, dyspnœa, etc.), and the tendency to hæmorrhage from the intestines which it produced, made us abandon its use."

Can anyone find an earlier reference to salicylate-induced gastrointestinal bleeding?

Pathological Laboratory,
River Hospitals,
Joyce Green,
Dartford, Kent. J. C. BURNE.

INDUSTRY AND PROFESSION

SIR,—Your leading article of Aug. 19 is in the main a sober and objective exposition of the relations between the pharmaceutical industry and the medical profession, and it is very difficult to quarrel with many of the views expressed. Nevertheless, at one or two points the reader seems to be invited to draw inferences which are quite unjustified. The article, for instance, contains the statement that "clinical trials should be strictly academic and judicial". Now, as a worker in the pharmaceutical industry I do not know of any clinical trials whatever which have not been "strictly academic and judicial". The situation is that highly qualified medical people employed by the pharmaceutical company decide that a clinical trial on a new drug would be justified and these members of the medical profession then approach the best independent medical experts on the specific subject with a request for such clinical trials. Unless and until the independent medical experts agree that worthwhile results are obtainable by the new drug, no marketing is undertaken. What more can the pharmaceutical company do?

Also the statement occurs "nowadays manufacturers often find themselves deciding without good enough evidence". If this statement is anything more than a rather careless remark, one would like to have examples. I suspect that the number of quotable examples would not justify the use of the word "often" to say the least.

The pharmaceutical industry, as we know it today, is a post-war development, broadly speaking. Many new industries behave in a rather raw manner in their early days and maybe the pharmaceutical industry has been no exception. Also in Britain we have in the "pharmaceutical industry" over one hundred companies, many owned by foreign parent companies, and differing greatly in size, kind of operations, policy, and aspirations. It is not surprising that among this heterogeneous mass of industry there is a lack of uniformity of behaviour, or that some of the companies behave in a way that is not wholly acceptable to the medical profession.

This is why it is foolish to make generalisations about the pharmaceutical industry. There are very few observations which apply to the whole of the industry. For instance, in your leader which I have mentioned you say: "Some observers believe that the industry's chief need is to divert its research towards making really new discoveries..." This comment has no sense when applied to some companies in the industry whose entire research is directed towards making really new discoveries, and has no application to other companies who carry out no research at all.

May I invite the editorial staff of *The Lancet* to come to see how this small part of the pharmaceutical industry plans its research, arranges its clinical trials, and decides whether or not to market a new drug? You would be perfectly free to report in your journal any opinions which you gained.

May I further invite, through your columns, any medical practitioner who detects any objectionable behaviour of any sort by us to write and tell us about it?

S. HOWARD
Division Chairman.
Wilmslow, Imperial Chemical Industries Ltd.
Cheshire. Pharmaceuticals Division.

POLYLOGUE ON PRACTICE

SIR,—Dr. Franklin (Sept. 2), while recognising the need to learn more about the management of psychiatric illness in general practice, admits his failure to gain any inspiration from the Polylogue on Practice (July 29). He states that the doctors attending similar seminars elsewhere "discuss only details of psychotherapy and the handling of the doctor-patient relationship" and feels that they should extend their range to the study of the natural history of common psychiatric syndromes, and to the evaluation of modern methods of psychometry, other therapeutic techniques, and drugs in use for mental stress.

All these are admirable projects for study, but not in the seminars mentioned. Some of the practitioners, who have taken part in similar projects in the past, have found the results of limited value in helping them to recognise and deal with the innumerable problems that beset them in their practices and have turned elsewhere for inspiration. These practitioners, who have considered psychiatric illness to range from severe psychosis to mild neurosis, and from grossly abnormal behaviour to mild somatic symptoms of psychological origin, have also, like Dr. Franklin, felt the need for new techniques and new tools to help them, but, unlike him, have found what they were looking for in the seminars held at the Tavistock Clinic and the Cassel Hospital.

What happens in these seminars? The practitioner, who has known how to deal with the organic aspects of his patient's disease at home, brings the mental aspects of the dis-ease to the seminar. Here the patient's mind is put up for inspection—his thoughts and feelings, his fears and hopes, his associated ideas, his patterns of behaviour and the circumstances in his life that may have determined those patterns. Naturally, at first, when the practitioner presents his patient's mind to the seminar, his own mind comes up for inspection too, because he tends to see his patient's mind in his own image. Later, however, the continued work in a seminar leads to a slight change of personality in the doctor, so that there is less distortion in the presentation of a case and a greater ability of the other doctors present to observe the patient's mind with the same accuracy which they have been taught to bring to the physical examination of the nervous system. In these seminars the doctor also learns how to study his patient as a whole person, rather than how to recognise and classify a vast number of syndromes into

1. Dreschfeld, J. *in* Allbutt's System of Medicine; vol. I, p. 851. London, 1905.

which he must attempt to fit his patient. Out of this somewhat blind approach to diagnosis and therapy, classification and therapeutic skills slowly emerge and develop, and these can be measured and tested in the usual scientific way.

What is the result of the seminars on the doctors participating? Instead of expecting to learn the management of psychiatric illness by the recognition of syndromes, and by acquiring the knowledge of standard techniques and of the use and abuse of drugs, the practitioner learns to use himself in a new way. Instead of making the patient answer a lot of questions, the practitioner is able to sit quietly and listen to everything the patient is trying to say; instead of accepting every word the patient says as a true expression of what he is trying to convey, the practitioner learns to interpret the language the patient is using to express his unconscious fears and fantasies and "mustn't-be-mentioned" needs; instead of prescribing nerve tonics for tiredness and wondering why the patient returns week after week for a repeat prescription, the practitioner learns better how to recognise and deal with the problem underlying the tiredness; and instead of referring all his intractable cases of backache and irregularity of periods for orthopædic and gynæcological investigations, the practitioner is able to sense which of those are due to mental stress, and so relieve both the surgeon and the patient of an unnecessary manipulation or operation.

There is, of course, a great need for general-practitioner research in the fields of study mentioned by Dr. Franklin, but this could only be carried out in a different setting. In the type of seminar mentioned, but not fully understood, by Dr. Franklin, a large number of doctors are gaining renewed interest in their work as general practitioners by learning a new approach to the recognition and understanding of their patient's problems. They find they can learn something about the patterns of behaviour which underly and explain so many of their patients' complaints, which were previously inexplicable, and they find they can offer more help than they were able to give in the past to those suffering from the misery and dis-ease of mental stress. Finally, they feel they can practise good preventive medicine by their early recognition and treatment of mental stress.

London, W.8. H. STEPHEN PASMORE.

EUTHANASIA

SIR,—Dr. Colebrook (Aug. 26), in juxtaposing the ambiguous statement that "medical men have admitted that they have taken steps to cut short a patient's suffering" and the statement that "even the Pope has declared that a doctor's first duty is to relieve suffering, even if by so doing the patient's life is shortened", would make the Pope appear to lend support to Dr. Colebrook's advocacy of euthanasia.

While nobody would quarrel with the concept of euthanasia in its true meaning (easy or comfortable death), the meaning given to it in this correspondence, and generally, appears to be murder by doctors, which is unthinkable.

Should euthanasia in this sense ever be permitted, no person thinking himself to be seriously ill would feel safe in entering hospital or perhaps even in consulting a doctor.

Dr. Ann Mullins (Aug. 26) refers to the pamphlet, The Case for Voluntary Euthanasia, saying that, "of the fifty-seven people with whose approval the pamphlet is issued, not one is either a general practitioner or a nurse". A possible explanation of this is that none could be found to support it.

Gaillimh, Ireland. S. UA CONCHUBHAIR.

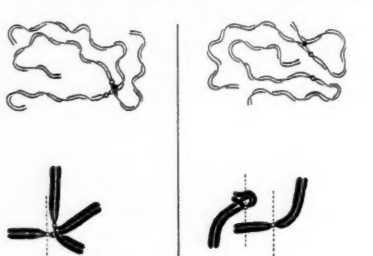
CHROMOSOMAL ABNORMALITIES IN WALDENSTRÖM'S MACROGLOBULINÆMIA

SIR,—Grossly abnormal chromosome complements have been reported for an aberrant cell population in Waldenström's macroglobulinæmia by Bottura et al.[1] and by German et al.[2] (one case each). They have in common, besides an apparently normal complement, a large chromosome, which is unlike any normal one.

German et al. discussed several possible interpretations. One was that the chromosomal abnormality resulted from whatever causes the disease. Though it is certainly conceivable that a biochemical disturbance should induce chromosome breaks, it would be a very strange coincidence if this had led in both cases to such a similar result. Why do none of the smaller chromosomes show evidence of a rearrangement? I find it no less difficult to accept that the two abnormal chromosomes should be entirely unrelated and yet cause the same disease. Thus I would tentatively take for granted that another possibility cited by German et al. applies: "that similar portions of a specific chromosome, perhaps the long arm of 2, may be involved in each case." But I would substitute "most likely" for "perhaps". It is only when we interpret the extra chromosome described by German et al. as an isochromosome consisting of two long arms of chromosome 2 that we get along with a minimum of breaks, be it a misdivision of the centromere or one break each in two no. 2 chromosomes leading to whole-arm transfer.

If the above interpretation of the one extra chromosome is correct, and if the two extra chromosomes have a segment in common, the extra chromosome described by Bottura et al. would almost have to be interpreted as a chromosome 2 in which the centromere was shifted towards one end by a pericentric inversion. At first glance one is puzzled by the question why the chromosomal rearrangement was followed in both cases by mitotic non-disjunction resulting in 47 chromosomes. To assume a mere coincidence appears far-fetched. My purpose is to show that there is a cytologically plausible

1. Bottura, C., Ferrari, I., Veiga, A. A. *Lancet*, 1961, i, 1170.
2. German, J. L., Biro, C. E., Bearn, A. G. *ibid.* July 1, 1961, p. 48.



The likely origin of the extra chromosome observed by German et al.[2] (a) and by Bottura et al.[1] (b).

Top.—Interphase: two no. 2 chromosomes; black dot, chromatid breaks and reunion. *Middle.*—Metaphase. *Bottom.*—Anaphase and, drawn separately, the result of non-disjunction for the "upper" daughter nucleus—an abnormal chromosome in addition to two normal no. 2 chromosomes [in the "lower" daughter nucleus the deletion of both long arms of no. 2 (*a*) is likely to act as cell-lethal, and so might monosomy for no. 2 (*b*)].

mechanism which could achieve this result. It is also the only mechanism I can envisage which is at all likely. It involves chromatid breaks and is illustrated in the accompanying figure.

In the one case (*b*), the close association of chromatids would probably preserve the inversion loop until the beginning of anaphase. The high degree of crowding characteristic of human metaphases, in conjunction with the mechanical difficulty of chromatid separation imposed by the loop, makes non-disjunction a likely outcome. This is also likely in the other case (*a*) in which two centromeres are kept in close proximity. This could, for instance, lead to a misorientation of one of them resulting in its failure to attach to the spindle.

If the above hypothesis should be correct one question still remains. Does the biochemical effect result from the presence in triplicate, or even in quadruplicate, of a single gene or of several genes so that a major part of the long arm of chromosome 2 must be present in addition to the normal complement? If only one gene locus were involved we should expect cases of the disease with 46 apparently normal chromosomes, a sufficiently small insertion being undetectable by the microscope. Occasionally a case should be found in which on one of the 46 chromosomes a small extra piece is recognisable. On the other hand, if almost the whole long arm were involved, all future cases should show a strikingly abnormal chromosome.

Departments of Medical Genetics and Pathology,
University of Wisconsin Medical School,
Madison, Wisconsin, U.S.A. KLAUS PATAU.

MUSCULAR DYSTROPHY AND DELETION OF Y CHROMOSOME

SIR,—Vaharu et al.[1] have described a case of enlarged phallus in a $4^1/_2$-year-old girl. She had gonadal dysgenesis and partly fused labia. 45 chromosomes plus a fragment were found in cells from blood-cultures. Conen et al.[2] reported a mosaic XO/XY with a deleted Y chromosome in the XY cells.

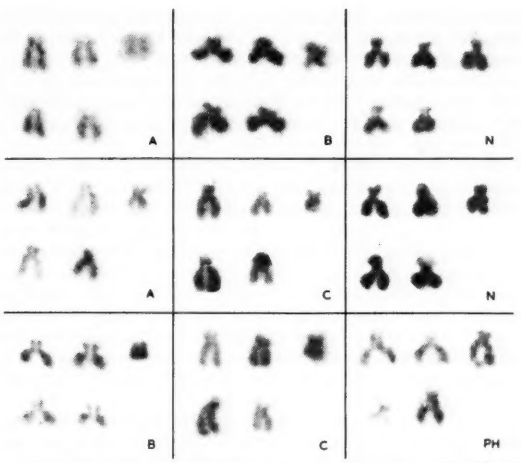
We have recently come across a family where five members suffered from muscular dystrophy, inherited apparently as an autosomal or X-linked dominant. In peripheral blood-cultures of the four males examined the Y chromosome shows a deletion comprising from a third to a half of the long arm of the Y chromosome. 3 of the males, the propositus, and his 2 small sons, showed hypospadias with mild manifestation (see accompanying figure).

The two adult males, the propositus and his unmarried brother, both showed an extremely low level of gonadotrophin.

It seems that the deletion of the Y chromosome in our cases is the cause of the hypospadias—considered to be a slight form of intersexuality, but is not sufficient to impair the fertility of the propositus. The case reported by Vaharu et al. suggests that the fragment present is a severely deleted Y. This deletion seems to involve both arms of the Y chromosome, leaving only the proximal part of the long arm plus centromere. The effect of this piece is to masculinise a basically Turner condition.

Thus various deletions of the Y chromosome give phenotypes which are intermediate between the fertile male and the Turner female. An increase in Y chromatin might be expected to cause excessive masculinisation, although in the balanced condition of sex chromosomes, the XXYY,[3] it seems to have no such effect. Both the XXY and the XXYY Klinefelters are clinically indistinguishable at present.

On the basis of the evidence it seems that the male determining genes on the Y chromosome are situated close to the centromere. Alternatively, one might envisage a system of pleiotropic masculinising polygenes located more or less randomly along the whole of the Y chromosome. At the moment we do not have any certain evidence of mendelian genes on the Y chromosome (due to lack of crossing-over between X and Y), but there are possibly genes controlling dimorphism in growth-rate between the sexes, genes controlling degree of infiltration into the embryonic gonads of primordial germ cells, genes controlling activity of embryonic testes, and possibly genes controlling "hairy ears"—a trait which appears Y-linked.[4]



Karyotypes of group VII (21, 22 and y) from: A, Propositus (43 yr.); B, his unmarried brother (46 yr.); C, youngest son (5 yr.); N, normal male; PH, male with chronic myeloid leukæmia showing the Ph-chromosome.

The study of deletions in the Y chromosome may enable us to localise some of these genes, or alternatively provide evidence of a polygenic system. These results will be published in more details elsewhere.

Cytogenetics Laboratory,
Christie Hospital and Holt Radium Institute,
Manchester. S. MULDAL
C. H. OCKEY.

PSYCHOLOGICAL TRAINING FOR FUTURE MIDWIVES

SIR,—I found your annotation of July 15 most interesting.

At the request of Miss Sheila Bramley, Matron of Bellshill Maternity Hospital, Lanarkshire, I introduced a group of three lectures on the psychological factors of midwifery to each school of pupil midwives as part of their training course, beginning at the end of 1959. It was perhaps significant that the request for these lectures came from the midwives themselves, since they felt that they were not fulfilling their nursing role completely since they lacked an understanding of the emotional problems of the pregnant woman.

The first lecture was concerned with body/mind relationships, and this was followed by descriptions of the defence mechanisms which by the ego deals with unconscious factors, all the time relating this to practical problems which the pupil midwives had seen in their own patients.

The second lecture was devoted to the common anxieties felt by the pregnant woman and how they could affect her behaviour, while the third lecture dealt with psychological problems in the labour room and in the puerperium, and psychiatric disorders arising in the puerperium were touched on very briefly.

At all times in the course it was emphasised that the information was being provided merely to help the midwife of the future to be more understanding of her patients and her

1. Vaharu, T., Patton, R. G., Voorhess, M. L., Gardner, L. I. *Lancet*, 1961, i, 1351.
2. Conen, P. E., Bailey, J. D., Allemang, W. H., Thompson, D. W., Ezrin, C. *ibid.* Aug. 5, 1961, p. 294.
3. Muldal, S., Ockey, C. H. *ibid.* 1960, ii, 492.
4. Gates, R. *Hum. Genet.* 1946, **1**, 13.

patients' needs; to implement the natural kindness and sympathy they had for the patient and to be aware of the impact of their own personalities on the patient.

It was always emphasised that this knowledge did not give them the right to become therapists, and it was made clear that their role should be only that of a tactful listener employing the American " uh-uh " technique.

The follow-up after the fourth course of lectures, when a considerable number of pupil midwives were interviewed to give their assessment of the course and suggestions for its future, showed that the information had been of great value and had given them some insight into the behaviour of their patients.

From my point of view, I felt that the lectures could do nothing but good, and I could not help noting that as a result of even those three specialised lectures pupil midwives had more practical information of psychological problems in obstetrics than had the medical students to whom I taught psychiatry in their 5th year of study.

The time allotted to teach medical students psychological medicine was far too short to deal in detail with obstetric conditions, which seemed a great pity.

Mental Hospital,
Parkside,
South Australia.

W. A. CRAMOND
Director of Mental Health.

IDENTICAL TWINS AND SELF-INFLICTED INJURIES

SIR,—I am anxious to learn of any identical twins who are severely subnormal and inflict distressing injuries upon themselves. If any of your readers know of such cases, in which one or both twins are affected, I would be very interested to hear from them.

Farnborough Hospital,
Kent.

P. N. SWIFT.

STEROID THERAPY IN JAUNDICE

SIR,—The very impressive paper by Dr. Williams and Miss Billing (Aug. 19) opens up a number of vistas. The hyperbilirubinæmia associated with hæmolytic disease of the neonate, and kernicterus, is a case in point.

Zetterström and Ernster [1] point out that the concentration-range in which bilirubin exerts its action on mitochondrial oxidative phosphorylation coincides very closely with the level (20 mg. per 100 ml.) which is known to be critical for the newborn infant. It has been suggested that 2-methylnaphth-1:4-ylene di (dihydrogen phosphate) ('Synkavit') may also uncouple oxidative phosphorylation.[2] Like many others, I have been intrigued by the fact that kernicterus is so definitely localised; according to Fisch and Norman,[2] nuclear jaundice occurs in an area which, in the newborn infant, may have the highest metabolic rate of all the structures in the central nervous system.

" Injections of albumin have been used experimentally to lower the bilirubin in [the serum of] jaundiced rats." [3] More effective means at an enzyme and metabolic level may be used to prevent brain damage from hyperbilirubinæmia instead of the present tedious technique of exchange transfusion.[4]

Dr. Williams and Miss Billing suggest that steroids may be found useful in the treatment of the Crigler-Najjar type of congenital hyperbilirubinæmia, where there is almost complete absence of glucuronyl transferase in the liver. There are also the other congenital causes of hyperbilirubinæmia, deficiency of glucose-6-phosphate dehydrogenase, with and without drugs; for which hitherto the only effective treatment has been replacement-transfusion. I would like to suggest seven things to help the Rh-positive fœtus when the mother has rhesus antibodies: (1) the husband should be genotyped; (2) fœtal cells identified in the circulation of the mother should be examined for their ABO group and rhesus state; (3) the amniotic fluid should be examined for the pigments that denote fœtal injury; (4) the cells in the amniotic fluid should be examined to determine fœtal sex, ABO group, and, if possible, the rhesus state of the fœtus; (5) steroid therapy should be tried to reduce the titre of rhesus antibodies in the circulation of the mother [5]; (6) the mother should be treated with 6-mercaptopurines to reduce agglutinins; (7) the newborn should be treated with steroids to reduce the serum-bilirubin level.

Pathology Department,
St. Margaret's Hospital,
Epping, Essex.

FRANK MARSH.

1. Zetterström, R., Ernster, L. *Nature, Lond.* 1956, **178**, 1335.
2. Fisch, L., Norman, A. P. *Brit. med. J.* 1961, ii, 142.
3. *Brit. med. J.* July 15, 1961, p. 163.
4. Hsia, D. Y.-Y. *in* Mental Retardation (edited by P. W. Bowman and H. V. Mautner). New York, 1960. (Proceedings of 1st Medical Conference, Portland, Maine.)

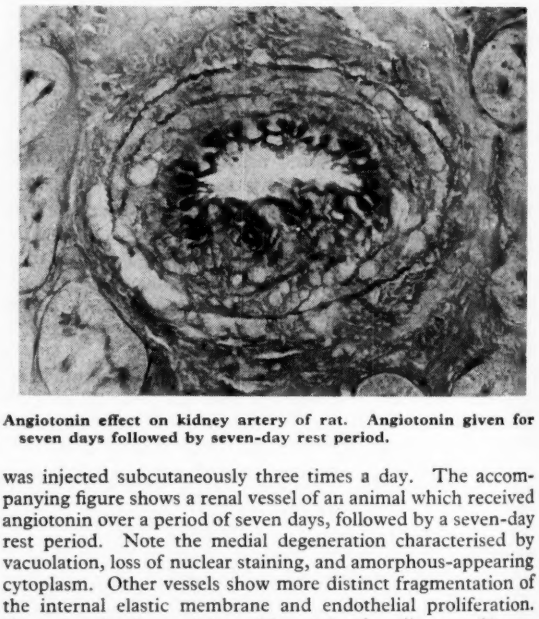
ANGIOTONIN AND THE KIDNEY

SIR,—We recently noted [6] that angiotonin (angiotensin) caused a marked diminution of the kidney pulse. It was suggested that the action of angiotonin on the renal vessels may comprise a link in the feed-back mechanism at work in hypertension, as follows:

RENAL "ISCHÆMIA"
(vasoconstriction)
↗ ↘
Angiotonin ← Renin

Subsequently we found that angiotonin, after a few days of injections in the rat, caused a big increase in the granulation and number of the juxta-glomerular cells giving support to this notion of a feed-back mechanism.[7] We wish now to describe changes induced in the vessels in the kidney of the rat by angiotonin.

Wistar strain albino rats weighing 250–275 g. were used. 2 μg. of synthetic octa-peptide form dissolved in 0·2 ml. saline



Angiotonin effect on kidney artery of rat. Angiotonin given for seven days followed by seven-day rest period.

was injected subcutaneously three times a day. The accompanying figure shows a renal vessel of an animal which received angiotonin over a period of seven days, followed by a seven-day rest period. Note the medial degeneration characterised by vacuolation, loss of nuclear staining, and amorphous-appearing cytoplasm. Other vessels show more distinct fragmentation of the internal elastic membrane and endothelial proliferation. Control animals receiving either 0·2 ml. saline or 20 μg. adrenaline in the same dose schedule failed to show these changes.

We suggest that these observations offer a possible explanation for the progression of vascular lesions in hypertension.

Departments of Medicine and Anatomy,
University of Southern California,
Los Angeles.

YALE J. KATZ
PAUL R. PATEK
SOL BERNICK.

5. Marsh, F. *Lancet*, July 15, 1961, p. 152.
6. Katz, Y. J. *ibid.* 1961, i, 1006.
7. Katz, Y. J., Patek, P. R., Bernick, S. *The Physiologist*, 1961, **4**, 56.

STAPHYLOCOCCAL INFECTION OF OPERATION WOUNDS

SIR,—We read with great interest the article of Sept. 2 by Dr. Forbes. We agree that there is no one measure which will overcome staphylococcal infection in hospitals and that a close surveillance of all operative and nursing techniques is required.

There are, however, many points in the article with which we cannot agree or which we believe to be unproved. The absence of contemporaneous controls is probably the major objection to the conclusions, but there is also an absence of definition of the criteria of infection, of the type of case included in the trial, and of a complete description of other variables in the series described.

At present a controlled experiment is being carried out in this department by the double-blind technique in a single operative procedure with other variables controlled, and this series will be reported in due course.

St. Mungo Department of Surgery, University of Glasgow, and Glasgow Royal Infirmary. ARCHIBALD L. GOODALL JULIUS L. STOLLER.

LEUKÆMIA

SIR,—I am prompted to write to you by the interesting series of discussions revolving about Dr. N. H. D. Schöyer's theory that leukæmia is due to an escape of the cells from inhibitory mechanisms.[1]

In 1952, I published data indicating that human white blood-cells contain an inhibitor of desoxyribonuclease. This inhibitor is present in mature cells and absent in immature cells.[2] It is present in highest concentrations in mature white cells of the blood-stream and in decreasing concentrations in white cells of the more immature forms of the marrow. Leukæmic cells, particularly the blast cells, contain no inhibitor whatever. In these papers I postulated that the inhibitor concentration is a function of maturity. The obvious implication being that immature cells and leukæmic, or malignant cells have many features in common, one of which is the absence of an inhibitor of this particular enzyme.

Dr. Schöyer's hypothesis that inhibitors of the white cell exist in the normal, and that leukæmia may be an expression of the escape of the white cells from an inhibitory mechanism, is of interest since my studies suggest the inhibitory factors may be present within the white cell itself. The leukæmia cell would then be a cell, which, for genetic reasons or otherwise, has lost its inhibitor. The consequences would be unrestrained proliferation without the maturation features characteristic of mature tissues.

Los Angeles, California, U.S.A. HENRY H. HENSTELL.

MEASUREMENT OF URINARY PROTEIN

SIR,—Like others,[3] we have used methods similar to those described by Dr. Lewis and Dr. Richards (May 27) for the measurement of urinary protein—i.e., the photometry of the degree of turbidity produced by a "protein-precipitating agent", commonly sulphosalicylic acid or trichloracetic acid. We agree entirely with the authors that the Esbach procedure is inadequate and should be discarded.

After using a turbidometric method for some time, we found that calibration with albumin is not quite accurate if the proteins lost in the urine are composed not only of albumin but of other serum-proteins also. Large errors may arise if the urinary protein consists of a paraprotein, such as Bence Jones'. A suitable simple procedure which allows quantitative determination of urinary protein regardless of its constitution consists in precipitating the protein (together with other material) with trichloracetic acid and then performing the biuret reaction, the precipitate being readily soluble in the reagent. So far, in all urines analysed by Kjeldahl procedures as well, the results of both methods have corresponded.

Since the usefulnesss of the combination of trichloracetic acid precipitation with the biuret reaction has repeatedly been reported,[4] we do not describe our method here. A full account is, however, available on request. It should be stressed that the method is no more time-consuming than turbidometry, since trial-and-error dilutions to find the protein concentration suitable for turbidometry are unnecessary.

Medical Policlinic, University of Munich, German Federal Republic. N. ZÖLLNER.

STEAM STERILISATION

SIR,—Dr. Fallon (July 1) has drawn attention to the variation in the steam-penetration times through loads in downward displacement sterilisers. Preliminary experiments carried out in the central sterile supply department, Musgrave Park Hospital, Belfast, indicate that a similar problem arises in the sterilisation of packs in high-vacuum high-pressure steam pressure sterilisers.

The tests were carried out in a fully automatic 60 c.ft. steriliser with an absolute vacuum of 20 mm. Hg and a sterilising temperature of 274°F for 5 minutes. The test pack consisted of six pairs of rubber gloves, each pair separately wrapped in paper and all six pairs wrapped in an outer cover of cotton balloon cloth. Four thermocouples were used, one in the chamber as control and the remaining three in one pair of gloves in the centre of the pack placed as follows: (*a*) tip of second finger; (*b*) centre of palm; and (*c*) in gauze swab in folded cuff. The maximum number of temperature readings which could be taken during the sterilising cycle was one thermocouple per minute, and the findings here reported are based on 15 test runs with the pack sited in different parts of the chamber.

The results indicate that:

(1) Considerable temperature differentials may exist inside a sterilising chamber following the introduction of steam. Initially during the sterilising period a thermal gradient exists between the outer cover of the pack and its contents. This gradient is rapidly reduced; but in certain parts of the pack, especially under the cuff and in the palm of the gloves, sterilising temperature was either not reached during the 5-minute sterilising period or was not sustained for long enough. It was also noted that different positions of the pack in the chamber showed different thermal characteristics. These findings were confirmed in two small bowl and instrument autoclaves; and it appeared that for a given size and shape of chamber the steam entry orifice and steam deflector plates largely determined the thermal characteristics of the steriliser.

(2) The lowest temperature point is not necessarily indicated by the thermometer in the chamber drain. Autoclave instrument and temperature recording chart readings showed a chamber drain temperature of 273°F during the sterilising period when thermocouples in the pack indicated temperatures of 266–271°F. During the same period the control thermocouple in the chamber indicated a temperature of 280-281°F.

(3) Pack contents may not reach sterilising temperature in the normally recommended exposure period of 3 minutes at 274°F, although instrument readings and graph records may indicate that the required temperature and exposure time have been attained.

The dryness fraction of the steam recorded during these tests was consistently good (0·98–0·97). The main difficulty encountered during the tests was that the maximum number of temperature readings which could be taken during the sterilising cycle was one thermocouple per minute. We consider that for the main investigation a multi-point recording potentiometer of high accuracy is essential; we have now obtained one.

1. *Lancet*, 1959, ii, 400, 447, 513, 569; 1961, i, 433, 559, 826.
2. Henstell, H. H., Freedman, R. I. *Science* 1952, **115**, 357; *Cancer Res.* 1952, **12**, 346.
3. King, E. J., Wootton, I. D. P. Micro-Analysis in Medical Biochemistry. London, 1956.
4. Harrison, G. A. Chemical Methods in Clinical Medicine. London, 1957.

These preliminary tests have been carried out on one comparatively small type of pack sited in different parts of an otherwise empty large chamber; it is proposed to conduct further tests with packs of varying size, and with packs in the partially filled and completely filled chamber.

The main implication of these tests is that high-pressure, high-vacuum sterilisers should before commissioning have their thermal-time characteristics determined in situ, in relation to the size of load and type of pack, whether drum, carton, fabric, or paper. Then steps should be taken to ensure that all loads conform to the requirements for sterilisation.

A further observation relating to the chamber capacity is important to hospitals planning the purchase of new steam pressure sterilisers. Specifications for steam pressure sterilisers provide either (*a*) the capacity in cubic feet of the chamber or (*b*) data from which this can be calculated. There is, however, from a practical point of view a difference between *nominal* chamber capacity and *usable* chamber capacity. The steriliser on which the above tests were carried out has a nominal chamber capacity of 60 c. ft., but the usable capacity is only approximately 30 c. ft.—i.e., 50% of the total capacity. This is due to the presence of rails for loading crates of dressings and to the fact that when loaded into the chamber the crates of dressings leave a considerable amount of unused space all round the periphery between crates and chamber wall, between upper and lower layers of crates or wire baskets, and between the rails and the floor of the chamber. It is probable that in lower-capacity chambers the relative amount of usable capacity will be increased. We suggest, therefore, that hospitals planning central sterile supply departments and the purchase of new sterilisers, the capacity of which is based on the estimated volume of loads per cycle or per day, should require manufacturers to provide data on the usable capacity of the steriliser chamber.

Engineer's Department,
Northern Ireland Hospitals Authority,
and
Musgrave Park Hospital,
Belfast, Northern Ireland.

H. F. HARRIS
V. D. ALLISON.

SIR,—In his letter of July 8 Dr. Marsh states that bags made from nylon film by heat-sealing are undamaged by the changes of pressure in a downward-displacement steriliser. This has not been my experience. It is true that the table in my paper (July 1) gives the results of two experiments where the bags showed no leak after sterilisation. However, eleven experiments had to be performed to provide the two results given, *because in all the others holes were present in the bags after sterilising.* These holes were detected by immersing the bags in water; once detected this way, the holes were usually easy to see—i.e., they were not mere pin holes.

These experiments were carried out with new film because it was found that after nylon film had been sterilised it was difficult to close satisfactorily by a heat-sealing process.

It is not difficult to see how bags could burst in a downward-displacement steriliser. If such a steriliser is opened when the steam has been exhausted to atmosphere after a sterilising run but before drawing the drying vacuum, the nylon bags will be seen to be ballooned. Any vacuum, even the relatively poor one produced by a steam ejector, would tend to increase this effect until the steam had escaped.

The method described by Dr. Marsh of using nylon bags in a high-vacuum steriliser is ingenious, but I cannot help wondering how effective a seal could be made round the aluminium tube which he suggests. The method of sealing described by Mr. Brigden (July 22) is simple and obviously functions well using a double forevacuum sterilising cycle where pressure changes take place relatively slowly. However, it would be interesting to see whether these packs would suffer the fate described by Dr. Edmunds (July 22) if they were placed in a high-vacuum steriliser. Also in a gravity displacement steriliser operated without a good double forevacuum air retention would occur in these packs unless they were positioned with care so that air could escape easily. Mr. Brigden mentions that he inspects nylon film for defects before use. Such defects may occur *in use*, and so the common practice of using nylon film as the only wrapper for a sterile article is much less wise than that of double-wrapping such articles.

Dr. Towers (Aug. 5) seems to have been much more fortunate than Dr. Edmunds in the results he has obtained with Browne's tubes in nylon packs. This may be due to a difference in the type of steriliser; and here it is important to emphasise that these tubes measure *quantity* of heat and not *quality*, and will change colour even when thermocouple tests show that air pocketing was present in the same load. If their limitations are recognised these tubes are, however, valuable indicators of a defect in sterilisation, and should be used not every 3–4 weeks but with every load. For high pre-vacuum sterilisers both Bowie [1] and I [2] have pointed out the desirability of monitoring conditions in the load.

Cloth and paper are less difficult wrapping materials than nylon and pass air and steam freely without the need for complicated sealing and positioning processes. Paper certainly is quite a good bacterial barrier for packs.[3]

Finally, I cannot quite see how Dr. Marsh believes that the pressure changes in the usual type of downward-displacement steriliser are as great as or even greater than in the modern high-vacuum steam steriliser, because this latter machine not only draws a much greater vacuum but is usually also operated at a higher pressure.

Department of Pathology,
Ruchill Hospital,
Glasgow.

R. J. FALLON.

SIR,—The reason why mixed packs of textiles and instruments often remain wet at the end of a vacuum/steam sterilising cycle is known although there is, as yet, no satisfactory solution to the problem.

Henry [4] has shown that the hydration and heating of textiles by dry steam, followed by their drying and cooling, is an almost reversible process. The high latent heat of vaporisation of water means that the degree of condensation needed to raise the temperature of textiles sufficiently for rapid sterilising is small, so that the drops of water which form are dispersed throughout the bulk of the material. In the post-vacuum stage, each small drop of water evaporates taking heat for this purpose from its immediate surroundings.

When steam condenses on solid objects the condensate tends to coalesce into larger drops which drain or soak away to a site where insufficient heat is available for their evaporation during the post-vacuum.

When the pre-vacuum, or post-vacuum, period is prolonged, some heat enters a solid object by conduction from the steriliser jacket so that, in the one case, it causes less condensation, and in the other, it assists evaporation. The advantage is slight if an object is embedded in the centre of a mass of fabric. Only when some part of it is close to the surface of a pack is the method of value.

Cracking open of the chamber door and purging with dry air is a revival of a method which has long been practised in downward-displacement autoclaves. The air acts as a thermal conductor from the jacket to the interior of the pack.

It seemed to us that if instruments and bowls could be wrapped in a material which was permeable to vapour and not to liquid water, wet dressings in mixed packs after sterilising could be avoided, although drops of water might remain inside the wrapping. But in tests with nylon cloth we found that condensation occurred on the outside of the wrapping where it touched the contents.

According to theory, if the entire surface, interior or exterior, of a solid object is in intimate contact with the surrounding

1. Bowie, J. H., 1961. Symposium on Recent Developments in the Sterilisation of Surgical Materials, London School of Pharmacy, April 11–13, 1961.
2. Fallon, R. J. *J. clin. Path.* (in the press).
3. Alder, V. G., Alder, V. I. *ibid.* 1961, **14**, 76.
4. Henry, P. S. H. *J. appl. Bact.* 1957, **22**, 159.

fabric, irreversible wetting could not occur unless the object had a high thermal capacity. Such contact appears difficult to achieve in practice. However, we have obtained good results with metal bowls by packing them in moulded cases of asbestos paper before wrapping them. Papier mâché about 1/4 in. thick would probably also be suitable.

In the case of the fluids steriliser, if the bottles are leaving the steriliser dry, we suppose that they are not cooled completely to room temperature and that the drops of water which adhere to their outer surfaces can obtain sufficient heat from the contents to evaporate.

Drying and Distillation Research Division, Edwards High Vacuum, Ltd., Crawley, Sussex.

T. W. G. ROWE
R. KUSAY.

PREGNANCY IN DIABETICS

SIR,—In your report of the congress of the International Diabetes Federation (July 29, p. 258), you state that "more evidence is accumulating from work on animals that maternal hyperglycæmia may prove diabetogenic to the fœtus in the absence of genetic factors. Dr. W. Gepts (Anvers) described the basis for this theory."

This is exactly the opposite of what I have said, and of what I have concluded from my experimental work. In the offspring of rats which had been made alloxan diabetic for 4 or 5 successive generations, I was unable to detect either a single case of spontaneous diabetes, or a reduction in glucose tolerance. The islet tissue of these rats, three months after birth, appeared to be completely normal.

These findings are at variance with those reported by Okamoto and Fukutome,[1] and by Bartelheimer and Kloos,[2] who did observe spontaneous diabetes in the offspring of alloxan diabetic rabbits and rats.

In view of these contradictory findings, the possibility of maternal diabetic hyperglycæmia being diabetogenic to the fœtus still seems open to question to me.

Anvers. W. GEPTS.

INSULIN

SIR,—Your leading article (July 8) fails to clarify the difference between the hydrogen atom and the hydrogen ion (proton).

You say: ". . . and two cysteine molecules readily give up their hydrogen *atoms* to suitable hydrogen acceptors to reunite as cystine under the catalytic influence of metal ions." You add later, "Essentially it involves the provision of energy through the catalysed transfer of hydrogen *ions* from primary substrates either to oxygen (as in aerobic respiration) or to a final hydrogen acceptor (as in anaerobic respiration or fermentation) . . ." What happens to the hydrogen electrons? Are they left behind with the substrate and are new electrons supplied to the itinerant protons at the end of the transport chain so that the newly formed atoms may be combusted by oxygen to produce water?

The most striking feature of diabetic coma is metabolic acidosis. When the bicarbonate stores of the blood become depleted, excretion of CO_2 by the lungs can no longer correct the tendency to acidosis and blood pH falls. The patient may then die of proton poisoning (just as patients in thyrotoxic crises may die of electron poisoning) and it is curious that a blood pH which is lower than the pH of water is seldom compatible with life. A patient in diabetic coma may sometimes be brought back to consciousness by large doses of insulin alone. Under these circumstances it would be interesting to know whether the blood pH was initially below the normal range, for then we could say that, whatever the intricate metabolism of ketosis, insulin administration had coincided with the release of electrons to neutralise the excess of protons.

1. *Tôhoky J. exp. Med.* 1954, **62**, 61.
2. *Z. ges. exp. Med.* 1952, **119**, 246.

"The more we learn about insulin the less we understand it." In-vitro studies indicate that the insulin-like activity of serum from diabetic subjects is able to transport or transform glucose more readily in fat than in muscle.[1 2] Perhaps the clinical reflection of this enigma is to be found in the observation that in young untreated diabetics muscle-wasting is prominent, whereas the diabetes of later life is more typically associated with excessive accumulation of depot fat. To treat obese diabetics with insulin is illogical; for this increases the appetite and leads to further fat synthesis, whereas the total withdrawal of carbohydrate from their diet commonly leads to weight loss and disappearance of glycosuria without further treatment.

The suggestion of Randle and Young [3] that —SH proteins may play a part in the transport of sugars into muscle should not be allowed to obscure the fact that unsaturated fatty acids form part of the structure of cell membranes. Is it not conceivable that the interconversion of, say, arachidonic and linolenic acids with appropriate transport of hydrogen may also contribute to the work of shuttling molecules between the cell and its environment?

The hearts of those who are chilled by chemical formulæ may be warmed by the words of Albert Szent-Györgyi [4]: "What drives life is thus a little electric current, kept up by the sunshine. All the complexities of intermediary metabolism are but lacework around this basic fact."

Canberra, Australia. S. B. FURNASS.

FAMILY CARE OF MENTAL PATIENTS

SIR,—Readers of your annotation of July 22 may also care to read about a Japanese Gheel at the village of Iwakura. The following description was given in 1912 by Dr. Frederick Peterson in the *Bulletin* of the Ontario Hospitals for the Insane (vol. **5**, p. 107):

"The third daughter of the Emperor Gosanjo in the eleventh century, developed melancholia in her eighteenth year. Word was brought to the imperial household that at Iwakura was a holy fountain, the water of which was healing to mental diseases and to disorders of the eyes. The emperor's daughter was taken there nearly 900 years ago and recovered and so brought fame to the temple and the well of Iwakura, as a result of which the insane were brought there in great numbers. At first three small inns were constructed to receive them, then later tea houses and villas and cottages sprang up in which to care for the ever-increasing influx of patients.

"In the year 1889 the village had 239 houses, with 1579 inhabitants, and up to that year one or two patients were received into each family to share in the occupations of the household, which were chiefly out-of-door employments in fields, gardens and forests.

"In 1889 the Japanese government, evidently under the impression gained from a study of the asylum systems of Europe and America, came to the conclusion that their colony system that had grown up so naturally was too far from our Western ideals, as exemplified in our colossal caravansaries for the insane, and so forbade the insane being any longer taken to the village of Iwakura.

"The result of this opposition of the government has been to reduce at least temporarily the number of insane in the colony. It is altogether likely that as soon as the authorities learn that out of themselves they have developed through nearly a thousand years the best of all methods of caring for the insane, toward which the West itself is struggling with much difficulty, they will remove the proscription and restore Iwakura to its ancient rights and privileges under State organization and inspection. There is one retreat for about 90 patients at Iwakura built on European models under the care of physicians,

1. Steinke, J., Taylor, K. W., Reynold, A. E. *Lancet*, 1961, i, 30.
2. Lowy, C., Blanshard, G., Phear, D. *ibid.* p. 802.
3. Randle, P. J., Young, F. G. *Brit. med. Bull.* 1960, **16**, 237.
4. Szent-Györgyi, A. Introduction to a Submolecular Biology; p. 22. New York, 1960.

to which excitable cases may be brought from the family homes in the neighbourhood."

It would be interesting to know whether any of your readers have first-hand knowledge of this institution.

Department of Health,
Parliament Buildings,
Toronto 5, Ontario, Canada.

CYRIL GREENLAND
Social Work Adviser.

HELLENOMANIA-HELLENOPHOBIA

SIR,—Dr. Jackson seems to imply in his stimulating article last week that trabecula, like data and diverticula, is a plural noun. If he does mean this, he has a mote (or rather a small beam) to cast out from his own eye, as it is certainly feminine singular. Moreover, phenomenon has always had in science and philosophy exactly the meaning "anything observed" that he deplores as a modern inaccuracy, and it is the implication of extraordinariness that is the colloquialism. But these are minor slips; all praise for his attack on misbegotten tetralogy and autopsy, and bastard roentgenology.

I think he underestimates the usefulness of Greek roots to a foreigner in enabling him to recognise at least some key words—for example, in the summary of a paper. Compare the German and Spanish versions of the same passage from the report of an international congress:

Am leichtesten sind Untersuchungen des Blutzuckers auszuführen, der von fast allen endokrinen Drüsen aus in charakteristischer Weise beeinflusst wird. Die Bilder zeigen die Blutzuckerkurven, die nach Bestrahlung der Hirnbasis, der Oberbauchgegend und der Keimdrüsen entstehen.

La irradiación de las glándulas endocrinas va seguida de ciertas modificaciones del nivel de azúcar en sangre, que evidencia curvas características. Después de la irradiación con onda corta de la base del cráneo, la curva de la glucemia adopta una forma definida, y lo mismo occurre después de la irradiación de la región abdominal superior o las gonadas.

Blutzucker = glucemia
Drüsen = glándulas
Bestrahlung = irradiación
Hirnbasis = base del cráneo
Oberbauchgegend = región abdominal superior
Keimdrüsen = gonadas

A reader equally ignorant of both languages but familiar with terms of classical origin in his own vocabulary would surely get the gist of the Spanish, but he would be puzzled by the more vernacular German.

By all means let the profession scrutinise candidates for its dictionaries as jealously as those for its Royal Colleges, but I think the lexicographers should keep up their Latin and Greek even though the physicians have dropped theirs.

Addenbrooke's Hospital,
Cambridge.

BRIAN WOODS.

SIR,—In reply to Dr. Jackson's enjoyable article, may I say something in defence of the word "thalassæmia", which has been translated by Sir Heneage Ogilvie as "sea in the blood".

I must admit that the word has always fascinated me. Perhaps it is the story of the long-continued shout "Thalassa" going back along the straggling lines of Xenophon's retreating Thousand when at last they reached the sea,[1] perhaps merely the association of Greece with the Mediterranean, but, nevertheless, the word sounds so much sweeter than "Cooley's disease" or "hæmoglobin-F disease".

Dr. Jackson shows commendable patriotism in his preference of "pituitary deficiency" to "panhypopituitarism", just as modern "chauvinistes" deplore the large number of English words added yearly to the French language. One must regretfully add, however, that the temptation to adopt foreign words goes back to classical times, and no less an exponent of Latin than Cicero made a regular habit of peppering his epistles with Greek!

Glasgow.

COLIN MAILER.

SIR,—May I congratulate my distinguished namesake, Dr. D. M. Jackson, on his admirable article? Without going all the way with him, I feel that the time is ripe for a *medical* word war to be fought on the lines laid down some years ago by Sir Alan Herbert in *Punch*. We must learn to use our Greek and Latin heritage with discretion: above all, we must purge our jargon of such misalliances as "perirenal". Could we, by the way, have the limerick about dysdiadochokinesis?

Crediton, Devon.

L. N. JACKSON.

ANTINUCLEAR FACTORS AND SYSTEMIC LUPUS ERYTHEMATOSUS

SIR,—In a preliminary communication last year,[1] Dr. Pollak and his colleagues reported that antinuclear factor had been found to be present in the sera of 24 out of 50 first and second degree relatives of 12 patients suffering from systemic lupus erythematosus.

During the course of a study of first-degree relatives of 24 cases of classical systemic lupus erythematosus we have observed the presence of antinuclear factor in only 4 sera of 81 first-degree relatives (89% completion-rate). These were compared with 81 sera from population studies in Leigh, Wensleydale, and Watford—matched for sex and age and tested concurrently. No positives were seen in the control group. All the tests were carried out on fresh frozen fœtal thyroid and the same antiglobulin conjugate was used throughout. Cryostat sections were overlaid with serum diluted to 1 in 10 and incubated for half an hour at 37°C, washed and fixed in 90% alcohol before staining with the conjugate (as described previously[2].)

Thus, although in our experience the relatives of patients with systemic lupus erythematosus show a higher incidence of antinuclear factor in their serum than the population at large, it does not approach that of Pollak and his colleagues.

Canadian Red Cross Memorial Hospital,
Taplow, Maidenhead, Berks.

B. M. ANSELL
G. D. JOHNSON
D. M. WEIR.

ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

SIR,—I was very interested to note the observation of Dr. Hilden and his colleagues (Aug. 12) that there was little difference between the mortality-rates of patients with myocardial infarction who had received anticoagulant therapy and those who had not. Please let me suggest, however, that physicians who contemplate changing (or omitting) therapy as a result of this observation should consider the following points:

(1) If a medical department of a hospital refrains for two years from using a drug generally believed to be of value, this may result in decreased confidence of staff members in the value of their ministrations and transmission of this decrease in confidence to patients. This is, of course, well known and is a basis for the common preference for "double-blind" experiments. Decreased confidence might be expected to be particularly damaging to patients recovering from myocardial infarction.

1. Anabasis, an account of the expedition under Cyrus the Younger of the Greek Mercenaries, referred to in *The Oxford Classical Dictionary* (1949).

1. *Lancet*, 1960, ii, 1061.
2. *Brit. med. J.* 1961, ii, 933

(2) The results of Dr. Hilden and his associates represent anticoagulant therapy controlled by the prothrombin and proconvertin (P & P) method of Owren and Aas and thus are not comparable with results representing therapy controlled by other methods. The five favourable reports mentioned in the fourth paragraph of the paper of Hilden et al. cannot represent the same sort of control since at least three of these reports antedate the publication of the P & P method.

(3) It seems likely that patients realised that medicine was prescribed at two hospitals and not at two others. Were some of them able to choose which hospital they would attend? If so, is it not possible that the more seriously ill patients would be less likely to be able to exercise this choice?

(4) Careful evaluation of the significance of this report requires a knowledge of the cause of death of patients who died of causes other than thromboembolism. If any significant number in either the treated or control groups died from clearly accidental causes, for instance, this would significantly affect interpretation of the results.

Englewood Cliffs, New Jersey.

MARSHALL E. DEUTSCH
Director of Life Sciences Research, Becton, Dickinson and Company.

MEMORIAL FUND FOR MARJORY WARREN

SIR,—The British Geriatrics Socity initiated and is supporting a fund to commemorate the pioneer work of the late Dr. Marjory Warren, consultant physician in geriatrics at West Middlesex Hospital, Isleworth, who was killed in a car accident in September, 1960. The object of the fund will be to finance scholarships, tenable in this country or abroad, to promote the study of the medical, nursing or social aspects of care and treatment of the elderly.

Dr. Warren, who was renowned not only in this country but in many countries overseas where she had lectured, advised, and helped, had in her lifetime, effected a revolution in the attitude towards the older patient in hospital and enabled many to be given the opportunity hitherto denied of "making the most of their capabilities within the limits of disability."

Donations should be sent to Barclays Bank, Ltd., 54, Highgate High Street, London, N.6.

AMULREE
President, British Geriatrics Society

JOYCE COCKRAM
President, Medical Women's Federation

OLIVE A. F. DAVIS
Chairman, South West Middlesex hospital management committee

ALAN MONCRIEFF
President, Institute of Almoners.

HAS MANKIND A FUTURE?

SIR,—I should like to support your plea for a truce to aggressive propaganda as a practical first step towards restoring normal relations between East and West. Both sides have now unloaded sufficient abuse on each other and the first to call a halt to this odious and undignified exchange will be rendering a direct service to the cause of peace. The proclaimed divergencies between the two main power groupings have now reached the stage of mutual paranoia and are viewed with increasing alarm and, one fears, disgust by many of the "uncommitted" nations. There may not be much time left before we reach the point when sane counsel can no longer influence the course of events. The resumption of nuclear tests is a portent of ultimate disaster which should shock people everywhere into a realisation that this generation is confronted with the greatest challenge man has ever had to encounter—that of how peace is to be preserved in a world where two great power groupings seem willing to resort to nuclear war rather than attempt to solve their problems soberly and sensibly and with some regard for human dignity.

Clare Hall Hospital, South Mimms, Barnet.

NORMAN MACDONALD.

Public Health

Prevention of Tuberculosis among Hospital Staff

THE Ministry of Health has circulated to hospital authorities a memorandum [1] containing advice on the prevention of tuberculosis among hospital staff. This advice was formulated by the Standing Tuberculosis Advisory Committee and has been endorsed by the Central Health Services Council.

Staff Generally

All hospital staff in contact with patients should be X-rayed before employment and normally at yearly intervals thereafter. A tuberculin test should be carried out on entry, and B.C.G. vaccination offered to those with a negative reaction.

Nurses

All nursing staff should be medically examined before being accepted as students or joining the staff. An X-ray of the chest should be taken at the same time and repeated annually as a routine. More frequent X-ray examination of nurses in tuberculosis wards should be a matter for the discretion of the medical staff responsible for supervising nurses' health. The risk of the disease developing can be substantially reduced by certain precautionary measures:

(*a*) Each nurse should be given a tuberculin test on entry and, if this is negative, should be offered B.C.G. vaccination.

(*b*) With student nurses this should be done before or as soon as possible after entry to the preliminary training school.

(*c*) Tuberculin-negative persons who refuse B.C.G. vaccination, if accepted for nursing at all, should not be allowed to nurse patients known to have tuberculosis. They should be retested at six-monthly intervals. When conversion occurs, exept as a result of B.C.G. vaccination, they should be referred to the chest physician.

(*d*) Nurses should be instructed in the precautions to be observed in nursing tuberculous patients.

Laboratory Workers

The memorandum reiterates the advice in the report of a special working party published in the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* in January, 1958.

Tuberculin-testing was recommended for all recruits; those with a negative reaction should be offered B.C.G. vaccination, and no recruit was to handle tuberculous material until the skin reaction was positive. All recruits should be X-rayed before employment and at intervals—perhaps annually—thereafter.

1. H.M. (61) 84.

Infectious Diseases in England and Wales

Diseases	Week ended August			
	5	12	19	26*
Diphtheria	1	2	..	3
Dysentery	314	253	266	242
Encephalitis:				
Infectious	1	2	1	3
Postinfectious	4	1	1	2
Food-poisoning	164	118	144	428
Measles, excluding rubella	8168	6281	4900	3479
Meningococcal infection	24	12	5	18
Ophthalmia neonatorum	14	18	14	20
Paratyphoid fever	4	3	3	4
Pneumonia, primary or influenzal	122	118	127	112
Poliomyelitis:				
Paralytic	14	19	19	14
Non-paralytic	4	4	6	7
Puerperal pyrexia	145	181	185	164
Scarlet fever	269	211	184	179
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	410	298	343	299
Meninges and C.N.S.	7	..	5	2
Other	57	36	62	40
Typhoid fever	5	6	4	4
Whooping-cough	307	296	315	290

* Not including late returns.

Obituary

KARL GUSTAV WILHELM NYLIN

M.D. Stockholm, F.R.C.P.

Prof. Gustav Nylin, a former director of the cardiovascular clinic of the Södersjukhus in Stockholm, died on Aug. 6. He was a past president of the European Society of Cardiology.

He was born in 1892, the son of a shoe manufacturer, and he studied medicine at the University of Uppsala. After qualifying in 1922 he settled in general practice in Spånga, and during the next eight years he carried out a series of physiological studies on children which were the basis of his M.D. thesis at Stockholm in 1930. He also collected valuable data on periodical variations in growth in children, standard metabolism, and the oxygen capacity of the blood. Finally he decided to give all his time to research, and in 1931 he became an assistant physician at the Royal Seraphim Hospital and two years later was appointed head of the physiological laboratory there. In 1935 he was appointed to a lectureship at the Caroline Institute. In 1937 he became chief of the medical clinic of the Sabbatsberg Hospital, where his research was centred on cardiovascular disease. He had already published many papers on blood-volume, and in 1945 he and his colleague Prof. Clarence Crafoord published their classical paper on resection in coarctation of the aorta.

In 1946 Nylin moved to the new Södersjukhus to take charge of the cardiological clinic there which he had helped to plan. Early in the '40s he had begun to use radioactive isotopes in his studies of the circulation (a technique of which he was one of the pioneers) and he later applied these to the cerebral circulation. In 1958 he was appointed chief of scientific research in the isotope laboratory at the Södersjukhus.

His work was well known outside his own country. His papers appeared in many European and American journals, and he was welcomed at congresses all over the world. In 1952 he presided in London over the first congress of the European Society of Cardiology, of which he was one of the founders and which he once described as " this splendid companionship in cardiology ". In his presidential address he gave a masterly survey of the British contribution to cardiology as seen by a European who was an admirer of this country.

He received an honorary degree from the University of Recife in Brazil, and he was elected F.R.C.P. in 1955. He also led an active life outside the hospital and the laboratory; and, at any rate in his younger days, he was an enthusiastic gymnast, skier, and tennis-player. He was also a keen fisherman.

J. P. writes:

"Anyone meeting Gustav Nylin at Stockholm or at an international congress will remember him as a friendly and forceful character filling an important place in the proceedings. He was a brilliant contributor in the cardiovascular field. His name will always be associated with his early pioneer work with Crafoord on resection for coarctation of the aorta and with the application of the radioactive labelling technique to the study of blood volume and distribution. He was enthusiastic and optimistic in research, yet this was fully controlled by precise and careful method and by a clear intellect. A list of his publications to that date appears in a number of *Cardiologia* (1952, **21**, 203) dedicated to him.

" Nylin was a generous soul finding it natural to think and act for others, to place himself at their disposal, and so it was that he won the affection of a large circle of friends in all parts of the world. This he shared with a charming and gifted wife, Ingrid, daughter of a famous Swedish painter. Nylin and his wife were a vital pair with strong social feeling and they were devoted to fostering good international relations in the profession."

Professor Nylin married in 1921 Ingrid Bjorck, and there were two daughters of the marriage.

RAFFAELE BASTIANELLI

M.D., M.Ch. Rome, Hon. F.R.C.S., Hon. F.A.C.S.

Professor Bastianelli, who was for many years director of the Regina Elena Institute for the study of tumours, died on Sept. 1 at the age of 97. For the first thirty years of this century he was the foremost surgeon in Italy, and even after his retirement he led an active life, and when he addressed the National Italian Medical Congress some ten years ago he impressed everyone with his vitality and originality.

The third son of Dr. Guileo Bastianelli, he received a classical education in Perugia and studied medicine in the University of Rome. Soon after qualifying in 1887, he joined the staff of the Policlinico in Rome, and rapidly became well known for his skill as a surgeon and his outstanding capacity as a teacher. In his wards there, in 1910, he introduced English nurses who became a nucleus of English nursing and teaching. In the 1914–18 war he served for three years in a front-line surgical unit, where he did pioneer work on the treatment of wounds of the head, chest, and abdomen. He made many English and American friends and was elected an honorary fellow of the English and American Colleges of Surgeons. In 1927, after 25 years of teaching, first as associate professor and later as professor of clinical surgery, he was presented with a *Festschrift* composed of contributions made by many of his colleagues and former pupils. In 1928 he was elected an honorary fellow of the Royal Society of Medicine in London.

Z. C. writes:

"Bastianelli was a general surgeon, for nearly all his work was done before surgery was split into water-tight compartments, and he wrote authoritative articles on the surgery of the brain, the tongue, the abdomen, and the urinary organs. At the Rome meeting of the International Society of Surgery in 1927 he took part in the discussion on the surgical treatment of cerebral tumours. Bastianelli took a great interest in the study of the causes and treatment of cancer and was appointed director-general of the Italian royal institute for the study and cure of cancer. To the last year of his life he maintained an interest in the new developments in surgery.

"He was a man of broad interests for he skilfully managed a farm, for years piloted his own plane, collected pictures, and kept open house for the distinguished visitors who came from all parts of the world to see him operate. To everyone he was the very pink of courtesy. He married an American wife and paid several visits to America to visit the clinics of the brothers Mayo and other distinguished American surgeons. On his 90th birthday he received many greetings from his friends in this country."

Prof. PRESTON MAXWELL

Professor Maxwell's former colleagues at Newmarket General Hospital write:

" After distinguished service in the Far East, both as a doctor and as a missionary, Professor Maxwell returned to this country to settle in retirement in 1939. But the late war immediately followed and his services as a surgeon were eagerly accepted at the E.M.S. hospital at Newmarket, where he worked throughout the war and during the early years of the National Health

Service. Although his duties were shared with much younger men, he never failed to command their respect and confidence by his skill, wisdom, gentleness, generosity, and unfailing good humour. His lifelong interest in obstetrics and gynæcology led him to set up a unit at Newmarket which has grown and still flourishes on the foundations he laid.

"A deeply religious faith and sense of mission also had to be satisfied, and his work as a preacher sustained him and supported others to the very end of his life. He conducted the religious Sunday observance at Newmarket General Hospital for over twenty years, and he was a greatly respected preacher over many miles of the surrounding countryside.

"Of his work in the Far East we have little intimate knowledge, for he was a humble man: but great works cannot be hidden, and yet it should be better known that his achievements in China were of paramount importance. Among them, together with Professor Turnbull, he established beyond question of doubt the existence of fœtal rickets. His researches into bone deformities in Chinese women led him to find the cause of these in osteomalacia. This work was a model of what is now known as social medicine. He traced the onset of osteomalacia to pregnancy with its drain on the calcium reserves and to the tradition of the Chinese women, who forsook the sunlight of their youth for the shadows in the fulfilment of their duty in maternity. The results of his work must have prevented immeasurable suffering amongst the Chinese and indeed in all undeveloped communities.

"Those of us who knew him in his later years will feel the loss of a lovable lively character, a sympathetic doctor, a gifted preacher, and a truly great gentleman."

The maiden name of the late Dr. Sinclair Miller's first wife was given incorrectly in his obituary last week. She was Miss Norah Isabel Glendinning.

Births, Marriages, Deaths

BIRTH

FALLON.—On Aug. 31, at Glasgow Royal Maternity Hospital, to Valerie and Ronald Fallon, M.D., B.SC.—a third daughter, Alison Wendy.

Appointments

ATKINSON, R. E., M.B. Leeds, D.P.H. Glasg.: deputy M.O.H., Buckingham, and assistant county and school M.O., Buckinghamshire.

BEARD, R. G., M.CHIR. Cantab., F.R.C.S.: consultant surgeon, Guy's Hospital, London.

DUNKIN, L. J., M.B. N.U.I., F.F.A.R.C.S., D.A.: consultant anæsthetist, Newcastle upon Tyne hospital group.

DUNN, A. S., L.R.C.P.E., D.C.H., D.P.H.: assistant county M.O., Norfolk, and district M.O.H., Thetford and Swaffham.

FRENCH, P. R., F.R.C.S.: consultant in the orthopædic department, St. George's Hospital, London.

GISBURN, MARJORIE A., M.B. Sheff.: school M.O., Nottingham.

JONES, MARY A. C., M.B. Birm., F.R.C.S., D.O.: consultant ophthalmologist, hospitals at Mexborough and Sheffield and Rampton Hospital.

LAKE, H. F., M.B. Durh., D.O.: consultant ophthalmologist, Sunderland and South Shields hospital groups.

PICKARD, B. H., M.B. Lond., F.R.C.S., D.L.O.: consultant, E.N.T. department, St. George's Hospital, London.

POLLOCK, G. T., M.B. Aberd., D.P.H.: deputy M.O.H. and deputy principal school M.O., Stockport.

WEBSTER, GRACE A. M., M.B. Aberd., D.OBST., D.P.H.: assistant M.O., Ealing and Acton.

Leeds Regional Hospital Board:

ATKINSON, J. N., M.B. Leeds: trainee in medical administration.

BALL, D. R., M.B. Leeds, F.F.A.R.C.S., D.A.: consultant in anæsthetics, Bradford Hospital.

CRUMPTON, N. E., M.B. Durh., D.P.M.: consultant in psychiatry, Broadgate Hospital, Beverley, and associated outpatient clinics.

Notes and News

SNAKES AND SHARKS IN HONOLULU

THE Tenth Pacific Science Congress was held between Aug. 21 and Sept. 2 in Honolulu—the venue of the first meeting in 1920. The congress provides a unique opportunity for personal contacts between scientists interested in many different disciplines including agriculture, anthropology, sociology, biology, forestry, geography, geophysics, and medicine.

In the medical division, venomous and poisonous animals and noxious plants were considered in four sessions. Most of the work reported dealt with laboratory experiments, usually involving electrophoresis or chromatography. Fish toxins were discussed by D. W. HESSEL, F. GHIRETTI, E. J. SCHANTZ, L. FARBER, and P. A. LERKE: various fractions were mostly neurotoxic, acting peripherally. In a provocative paper W. G. GLENN reviewed venom research from the immunochemist's viewpoint: he doubted whether electrophoresis or chromatography would provide data of significant value. In reviewing clinical observations on 1167 snakebite patients studied during the past three years in Malaya, H. A. REID said that over 70% of the bites were due to the pit viper, *Ancistrodon rhodostoma*. The clinical effects in man might differ very significantly from those recorded in animals. Thus neurotoxic effects were most exceptional in cobra bites—local necrosis was the common symptom in man. Sea-snake venom was myotoxic.[1] An outstanding clinical feature was the large number of victims escaping with trivial or no poisoning—40% of 840 cases in which the snake was reliably identified as viper, cobra, or sea-snake. In half the *A. rhodostoma* victims, systemic poisoning resulted in a defibrination syndrome which persisted up to three and a half weeks in the absence of specific antivenene, which promptly corrected the clotting defect (with dramatic clinical improvement) even when given several days after the bite. M. BARME reported work on sea-snakes in Vietnam, confirming that many fishermen were bitten but rarely came to hospital. *Lapemis hardwickii* was the commonest species, and venom had been used to immunise a horse. The resulting antivenene also gave cross-protection against venoms of other common sea-snakes, such as *Enhydrina schistosa* and *Hydrophis cyanocinctus*.

Sharks were considered at four sessions in the marine biology section. Blinded sharks in captivity could still detect food with their well-developed olfactory organs (A. L. TESTER): they were attracted by fresh human blood at very low concentrations. Human urine neither attracted nor repelled sharks, but sweat was avoided. P. W. GILBERT reported low visual acuity (retinal cones are absent except in mustulus) but high sensitivity. At distances of 100 feet or less, vision became increasingly more important than olfaction, and at 10 feet or less was probably the principal sense involved in directing a shark to a target. When both vision and olfaction were obliterated simultaneously the shark swam helplessly around, injuring itself repeatedly, and died within three to five days. L. P. SCHULTZ analysed 799 shark-attack cases documented at the Smithsonian Institute. 50% (408) were fatal. Most attacks occurred when the greatest numbers of swimmers were in the water—near the shore. Thus, 25% were bitten within 50 feet of the water-edge, 30% within 51-200 feet, 25% at distances up to 2 miles, and 19% in the open sea. 70% were in the upper 5 feet of surface water. 19% were fishing, 69% swimming, and 7% clinging to a float; and 5% were attacked while rescuing another victim.

BANGKOK SCHOOL OF TROPICAL MEDICINE

ON Aug. 11 a School of Tropical Medicine and Endemic Diseases was formally opened in Bangkok by the Prime Minister, Field-Marshal Sarisdi Dhanavajata, before an audience including the Minister of Public Health, Dr. Phra Bomrajnaradoon. Prof. Svasti Daengsvang outlined the history of the creation of the school, including the part played by Prof. Brian Maegraith, dean of the Liverpool School of Tropical Medicine, and by the World Health Organisation. The Prime Minister, in his reply, spoke of the importance of the school for the health of Thailand and its potential significance as a centre for teaching and research in South-East Asia.

The school buildings, to be completed by 1963, will include a hospital for endemic diseases. Teaching for the diploma in tropical medicine and hygiene (Bangkok) began last year, with a course lasting six months which is designed to cover the diseases of South-East Asia, and Thailand in particular, with

1. Reid, H. A. *Lancet*, Aug. 19, 1961, p. 399.

emphasis on the countryside and on prevention. The research of the school covers endemic conditions such as liver-fluke infection, paragonimiasis, and the epidemiology of the focus of *Schistosoma japonicum* infection recently discovered by the school staff in South Thailand. Physiological aspects of disease processes including diarrhœal diseases are also being studied. Further developments on these lines will include the use of a wide range of radioactive isotopes.

The school is staffed by Thai doctors, most of whom have worked at some stage in Europe or the United States. The dean is Dr. Chamlong Harinasuta, already known in other countries for his work on opisthorciasis, schistosomiasis, and amœbiasis. There is to be a close liaison with the Liverpool School of Tropical Medicine.

INTERNATIONAL SOCIETY OF UROLOGY

THE twelfth congress of the Société Internationale d'Urologie was held in Rio de Janeiro from July 24 to 29 under the presidency of Prof. Figueiredo Baena. This was the first occasion on which the society had met in the Southern Hemisphere, and three hundred members from thirty-five countries were present.

The first three days of the meeting were devoted to discussions on the Late Results of Reparative Operations on the Ureter, the Effect of Pelvic Irradiation on the Urinary Tract, and the Treatment of Vesical Exstrophy. Mr. A. W. Badenoch reported on the Surgical Treatment of Tuberculous Stricture of the Ureter. The remainder of the congress was taken up with free communications on urological subjects to which British members contributed as follows: Mr. J. D. Fergusson, X-ray Television in Urology; Mr. Howard G. Hanley, Cavernotomy; Mr. W. S. Mack, Varicocele and Male Infertility, and Renal Injuries; Mr. R. Mogg, Tumours of the Lower Urinary Tract in Children; and Mr. T. Moore, The Female Prostate.

The next congress is to be held in London in 1964.

After the congress Mr. J. D. Fergusson, director of Teaching and Research, Institute of Urology, visited Lima and Caracas under the auspices of the British Council to lecture and take part in clinical demonstrations.

Medical Research Council

The Council are to set up a research group on demyelinating diseases in the University of Durham at the William Leech Research Laboratories, Royal Victoria Infirmary, Newcastle upon Tyne, under the direction of Dr. E. J. Field. Dr. Field is senior lecturer in neuropathology at King's College Medical School and consultant neuropathologist at the Infirmary. Dr. H. G. Miller, physician in neurology to the Infirmary, will act as an advisor on the clinical side.

From Sept. 18 the Council's headquarters will be at 20, Park Crescent, Regent's Park, London, W.1 (MUSeum 5422).

Feldberg Foundation

Prof. W. Feldberg, F.R.S., a senior member of the Medical Research Council's scientific staff at the National Institute for Medical Research, has set up a Foundation out of funds awarded to him by the Federal German authorities as compensation for professional damages.

It is to be known as the Feldberg Foundation for German-English Scientific Exchange for Experimental Medical Research and will be administered by a board of directors consisting of three German and three British scientists. Each year the Board will award a prize to one German and one British research worker. The German recipient will give a lecture in Britain and the British recipient a lecture in Germany. The German Federal Republic have conferred the Grosses Verdienstkreuz on Professor Feldberg in recognition of this endowment.

The prizewinners for 1961 are Sir Lindor Brown, Waynflete professor of physiology at the University of Oxford, and Prof. Herbert Hensel, director of the Physiological Institute of the University of Marburg. In November Professor Hensel will lecture at University College, London, on the electrophysiology of thermoreceptors, and Sir Lindor Brown will lecture at Heidelberg on the adrenergic neurone.

London Hospital Medical College

Dr. William Evans will give a Schorstein lecture on Friday, Oct. 13, at 4.15 P.M. in the College Hall, Ashfield Street, E.1. His subject will be cardiology at the London Hospital. Tickets may be had from the secretary at the college, Turner Street, E.1.

Association of Anæsthetists of Great Britain and Ireland

The annual meeting of this Association is to be held from Oct. 18 to 21 in Dublin. Further particulars may be had from the secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2.

Drug Action and Modern Therapy

The Anglo German Medical Society is holding a symposium on this subject at 1, Wimpole Street, London, W.1, from Sept. 28 to 30. The subjects chosen for discussion are: oral antidiabetic agents, anabolic and gestational steroids, modern drugs used in psychiatry, and side-effects of drugs. Doctors who are not members of the society may apply for tickets to Dr. E. Kawerau, department of pathology, St. James' Hospital, Balham, S.W.12.

Chest and Heart Association

This Association is to hold a symposium under the chairmanship of Prof. F. R. H. Heaf on Wednesday, Oct. 18, at 2 P.M. at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, on the eradication of tuberculosis in childhood. A conference on stroke rehabilitation is to take place in Birmingham, on Thursday, Nov. 16, at 2 P.M. under the chairmanship of Dr. Ernest Bulmer. The third Health Conference for Executives will be held on Thursday, Nov. 30, at 10 A.M. at the Connaught Rooms, Great Queen Street, London, W.C.2. Particulars about these meetings may be had from the Association, Tavistock House North, Tavistock Square, London, W.C.1.

Major-General J. C. Barnetson has been appointed deputy director-general Army Medical Services, at the War Office.

100 medical schools are listed in the new edition of *Admission Requirements of American Medical Colleges*. 86 are in the United States and Puerto Rico, 12 in Canada, 1 in Beirut, and 1 in the Philippines. Copies of the book ($2 post paid) may be had from the Association of American Medical Colleges (Dept. 2B), 2530, Ridge Avenue, Evanston, Ill.

CORRIGENDA: *Long-term Anticoagulant Therapy*.—In this leading article, lines 5 and 6 on p. 140 should have read: " . . . even by Owren's estimate, there are about 100,000 potential patients in this country now."

Possible Absence of Essential Hypertension in Two Complete Pacific Island Populations.—In this article by Dr. I. Maddocks (Aug. 19, p. 396), fig. 2 and the accompanying legend were incorrect. The correct figure and legend are shown below.

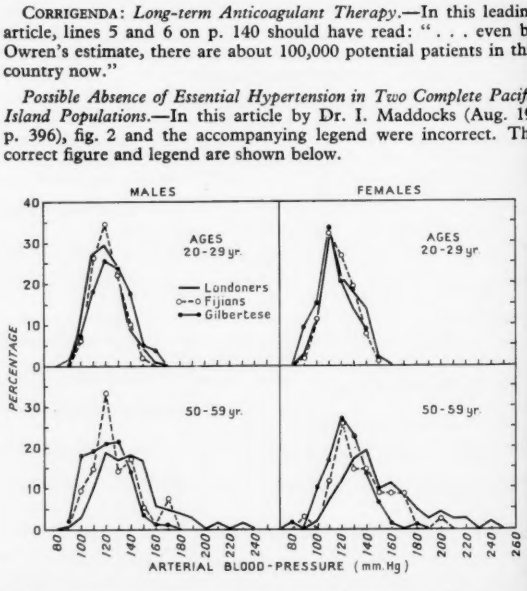


Fig. 2.—Frequency distributions of systolic pressures of both sexes in the third and sixth decades of a London population (Hamilton et al. 1954), Fijians, and Gilbertese.

NCET

riday,
, E.1.
ckets
, E.1.

land
from
from
ields,

sium
from
: oral
odern
octors
ets to
spital,

rman-
2 P.M.
s Inn
sis in
take
under
Health
v. 30,
Street,
e had
istock

deputy
e.
mission
United
in the
om the
Ridge

eading
ven by
in this

Pacific
ug. 19,
t. The

n sexes
milton